

THE DISCOVERY OF INSULIN

at the

UNIVERSITY OF TORONTO



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HAVE THEY ROBBED DIABETES
OF ITS TERRORS



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An exhibition
commemorating the 75th anniversary
by Katharine Martyn
With an historical essay by Michael Bliss
and an
Introductory preface by Mladen Vranic



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FOREWORD

The Thomas Fisher Rare Book Library is delighted to participate in the celebration of the 75th anniversary of the discovery of insulin by presenting this exhibition and catalogue. Few scientific breakthroughs have achieved the legendary status of the experiments carried out by Banting and Best during the hot summer months of 1921 in the laboratories, and on the roof, of the old medical building at the University of Toronto. The effects of the discovery were so dramatic, with children saved from certain death, that the public imagination was captured immediately and the story still retains its emotional force. Inevitably several stories, some of these conflicting, grew up and it was not until Prof. Michael Bliss published his book, *The Discovery of Insulin* that the real contributions of Banting, Best, Macleod and Collip were sorted out and made coherent.

The Fisher Library is fortunate to possess many of the original documents from which the original experiments can be reconstructed, and additional material has been borrowed for the exhibition from Dr. Henry Best, who generously lent documents and photographs from his collection of his father's papers, from the Academy of Medicine collection (now at the Fisher Library), the University of Toronto Archives, and the Connaught Laboratories.

We are grateful to Prof. Bliss, who has written a new account of the discovery especially for this catalogue, for his encouragement and support. Prof. Mladen Vranic, of the Department of Physiology, who was originally hired by C.H. Best, has also written a brief history of his department. Katharine Martyn has effectively used much of her sabbatical leave to organize the exhibition and write the catalogue.

Eli Lilly Canada Inc., the organizers of the 1996 International Research Symposium on Diabetes, and the Friends of the Thomas Fisher Rare Book Library are warmly thanked for their financial support of the exhibition and catalogue.

Richard Landon
Director,
Thomas Fisher Rare Book Library



J.J.R. Macleod, Chairman of the Physiology Department, University of Toronto, 1924.

THE PHYSIOLOGY DEPARTMENT, UNIVERSITY OF TORONTO, 1887-1921

This year marks the 75th anniversary of the discovery of insulin, which is being celebrated in Toronto with an International Symposium, hosted by the Banting and Best Diabetes Centre, University of Toronto, and The Toronto Hospital, in collaboration with the Joslin Clinic, Boston and the Karolinska Institute, Stockholm. This collaboration extends the previous tradition in which the University of Toronto and Karolinska Institute co-organized a number of international insulin symposia. As a former post-doctoral fellow and friend of Charles Best, and as a former Chairman of the Department of Physiology, I have been asked, and indeed it is a privilege for me, to give a brief history of the Department before the discovery of insulin and so to recognize those pioneers of physiology who set the stage for one of the most dramatic discoveries in medicine.

It is not by chance that in 1921 insulin was discovered in the Department of Physiology at the University of Toronto. Physiology has a very strong tradition in research and teaching stretching back more than 110 years to the renowned educator Ramsay Wright. Ramsay Wright was born in Alloa, Scotland in 1852 where his father, a scholar, was minister of the Free Church of Scotland. Young Ramsay Wright studied medicine for three years, confining himself largely to its scientific side, and graduated with a B.Sc. At the age of 22, he was appointed Professor of Natural History at the University of Toronto, a title later changed to Professor of Biology and Physiology. In 1887, when the new Medical School was established, Ramsay Wright directed Physiology for five years. He served as Vice-President of the University and Dean of the Faculty of Arts.

What is important in life sciences research is the proper training of research people in laboratory work. From the beginning, this was Wright's interest and his legacy. Together with Professor James Loudon, later President, he put into place a framework and established advanced facilities within the University of Toronto for the future of practical science instruction. Biological laboratories were established first in the School of Practical Science and later in the Biological Building, and a Biological Museum was added to serve as an adjunct to practical teaching.

In 1891, an independent Chair of Physiology was established, and it was Ramsay Wright's student, A.B. Macallum, who became its first incumbent. Macallum was born in 1858 on a farm in Westminster Township, Ontario, the son of Alexander Macallum, who came from Scotland in 1830 to pioneer in what was then bush country near London. A.B. Macallum obtained his undergraduate degree from the University of Toronto and his doctoral degree from Johns Hopkins in Baltimore. University of Toronto historian, Robin

Harris, notes that "Macallum's greatest contribution to the University of Toronto was the establishment of research and scholarship as essential functions of the University. In the 1880s, when he first joined the faculty, the University was a reputable teaching institution concerned with the preservation and dissemination of knowledge, but not with its advancement." He was certainly one of the most distinguished scientists that Canada ever produced.

Macallum localized ions which are responsible for maintenance of osmotic pressure in plasma and the cells and he was a pioneer in this field. He indicated that the concentration of the salt in blood plasma is similar to that of sea water of the Cambrian or Silurian period. Dr. Rothschild, in his book, *The History of Physiology*, indicates that "regarding the development of American chemical physiology, three figures can be justly considered as the founders of this physiological field: A.B. Macallum, R.H. Chittenden and W.O. Atwater". His work received world-wide recognition in the form of honorary degrees from Aberdeen, McGill, Toronto, Trinity College, Dublin and Yale. It was a landmark when he became the first University of Toronto graduate to be elected to the Royal Society. In 1908, a Chair of Biochemistry was established for Macallum at the University of Toronto — only the second of its kind to be established in the British Empire. He remained as Chairman until 1917, when he went on to become Chairman of Biochemistry at McGill for a further eight years. It is also notable that he was the first Chairman of the National Research Council in Canada.

Macallum's impact on the development of the Departments of Physiology and Biochemistry both at Toronto and McGill was enormous. He fought hard and completely succeeded in transforming the University of Toronto's Medical School, which the Royal Society considered as being "in the same condition as an English provincial school", into one of the leading schools in North America. There was also a fundamental change in the view of the University primarily as a teaching institution. Macallum's legacy was the recognition of research as a necessarily complementary function in all departments. This was engineered by the development of graduate studies at the doctoral level. Macallum supervised the first student to obtain his Ph.D. at the University of Toronto. "Macallum's monument is the Medical School of Toronto," stated his Royal Society obituary. Through the generosity of the Macallum family, the annual Macallum Lectureship was established in the Department of Physiology in 1976.

T.H. Brody succeeded Macallum as Chairman of the Department of Physiology from 1908 until 1916. As Macallum indicated, "Dr. Brody began to develop the Department along biophysical lines, with the result that at his death, the laboratory ranked among the three leading laboratories of physiology on either side of the Atlantic." Since his time,

physiological biophysics has been an important line of research in studies related to neurophysiology, cardiovascular, and respiratory physiology, and dynamics of metabolism. Brody was born in 1866 in Northampton, England, the son of Reverend Alexander Brody, Vicar of Grandborough. He studied Arts at the University of Cambridge and Medicine in London, England. He held positions in the Departments of Physiology in King's College London, London Hospital Medical School, and at St. Thomas's Hospital Medical School. At 36 he became a member of the Royal Society. He was considered one of the leading experimental physiologists of the English-speaking world but his work was abruptly stopped by his untimely death at the age of 50.

Following the death of Brody, J.J.R. Macleod became Chairman of the Department of Physiology (1918-1928). Macleod was born in Clunie, Perthshire, where his father was a Minister of the Free Church of Scotland. He finished Medical School at the University of Aberdeen and did post-graduate studies in Physiology at Leipzig, Germany and Aberdeen. He worked in Physiology and Biochemistry at the London Hospital Medical School. In 1903, at the age of 27, he became Chairman of the Physiology Department at Case Western Reserve University in Cleveland (1903-1918). When he came to Toronto, he was an expert in the field of carbohydrate metabolism and had done extensive work on factors that regulate blood glucose concentration, including the role of the nervous system, dietary factors, and the adrenal gland in liver glycogen control. He also did studies related to abnormalities of glucose utilization in diabetic dogs. It is of particular importance to note that in 1915 he published a paper entitled: "Rapid and accurate clinical method for the estimation of sugar in small quantities of blood." Establishment of this methodology in the Department of Physiology was undoubtedly critical in the work leading to the discovery of insulin.

When Macleod arrived in Toronto, he was one of the world's leading physiologists, with a particular reputation in the field of carbohydrate metabolism. He gained this reputation not only through his original publications, but also through the publication of a classic textbook, *Physiology and Modern Medicine*. With the experience gained in leading British and American Universities, Macleod was in a position to know what constituted a state-of-the-art Department of Physiology, and he worked to achieve those things he felt were essential to bring Toronto's Department of Physiology in line with other leading world institutions.

When Frederick Banting arrived in Toronto to begin his research, he found a Department of Physiology with a long history of outstanding scholarship fostered by many researchers, and international leadership in the field of carbohydrate metabolism. He found a department not only well-equipped to carry out the necessary experiments

*The old
Medical
Building,
University of
Toronto, 1920s.*



which led to the discovery of insulin, but one willing to gamble on an idea. In addition, he found a willing and enthusiastic student in Charles H. Best, who went on to become Chairman of the Department of Physiology in 1929, and continued the legacy for thirty-three years. The University of Toronto Charles H. Best Lectureship and Award was established in the Department of Physiology in 1995, through the generosity of John K. and Mary E. Davidson. As Robin Harris remarked, the discovery of insulin greatly raised the profile of and increased the emphasis on the importance of research, not only in the Medical School, but in other faculties as well.

The discovery of insulin had a strong impact on the development of the Department of Physiology. In addition to diabetes research, it has become a major focal point for key areas of physiology, using integrative, molecular and cellular methodologies at the cutting edge of research.

Mladen Vranic, M.D., D.Sc., F.R.C.P.(C)
Professor of Physiology and Medicine

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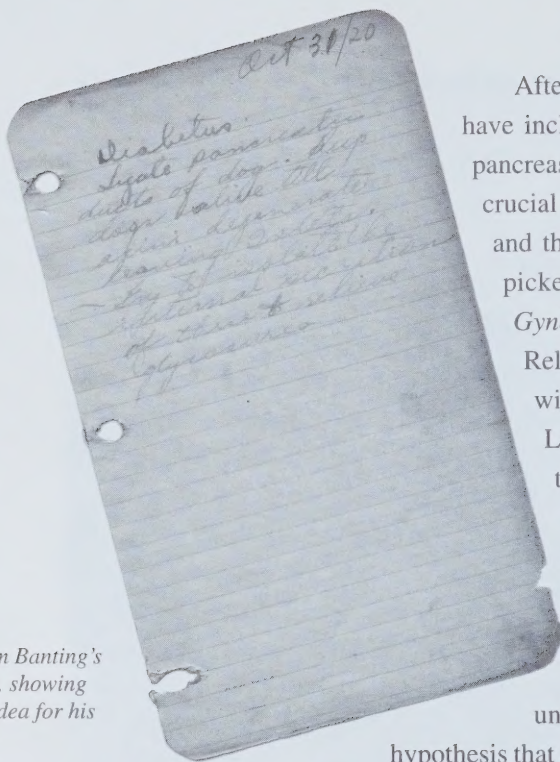
Birth of an Idea

One of the most dramatic adventures in the history of medicine had an inauspicious beginning in the office of the University of Toronto's Professor of Physiology, J.J.R. Macleod, on November 8, 1920. A shy, inarticulate graduate of the Faculty of Medicine, Frederick G. Banting, came to see Macleod to inquire about the possibility of using the University's facilities to test an idea he had for research on the pancreas.

It was not an easy interview. Banting had no experience at research and knew little about either the pancreas or the disease, diabetes mellitus, for which he hoped to find a treatment. Macleod doubted that the idea Banting was presenting would lead to positive results. But the exact procedures being suggested by Banting did not appear to have been tried by anyone else, and in that situation even negative results could be useful. Macleod was also in the happy position of having an under-used facility on his hands. After warning Banting that not much would probably come from the work, and that it would be best to wait until the next summer, he offered to let the young man work in his lab.

Frederick Grant Banting (1891-1941) was a farmer's son from the village of Alliston, Ontario, some 60 kilometres north of Toronto. He worked hard to scrape through secondary school and go on to attend Ontario's provincial university, the University of Toronto. He transferred from Arts into Medicine, graduated with above-average standing in the class of 1917, had already enlisted in the Canadian army, and by the summer of 1918 was treating casualties at front-line dressing stations in France as a battalion medical officer. He saw considerable action, and was eventually awarded the Military Cross for courage under fire, before being wounded by shrapnel.

Back in Canada, Banting served a year's residency in surgery at Toronto's Hospital for Sick Children, then set up practice in the small city of London, Ontario, some 175 kilometres west of Toronto. With time on his hands while he waited for the practice to build, Banting took a position as a demonstrator in surgery and anatomy at London's Western University. As part of that job, he had to give his students a talk on the pancreas on Monday, November 1, 1920.



Page from Banting's notebook, showing the first idea for his research.

After preparing the talk, which would certainly have included mention of the issue of whether the pancreas contained an “internal secretion” that was crucial to the control of carbohydrate metabolism and the prevention of diabetes mellitus, Banting picked up the newly-arrived issue of *Surgery, Gynecology and Obstetrics*. Its lead article “The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis” by Moses Barron, MD, discussed the consequences of blockage of the pancreatic ducts in a living subject. The pancreas atrophied or shrivelled, Barron reported, but the cell system in it known as the islets of Langerhans, did not. Since diabetes apparently did not develop in such cases, unless or until the islets were damaged, the

hypothesis that the elusive internal secretion of the pancreas originated in the islet cells seemed very strong.

Banting could not get to sleep that night. Eventually he got up and in a little notebook jotted down a date, October 30, corrected it to October 31, and then wrote

Diabetes
Ligate pancreatic ducts of dogs. Keep dogs alive till acini degenerate leaving Islets.
Try to isolate the internal secretion of these to relieve glycosuria.

This was the research idea Banting discussed with Macleod in Toronto eight days later. Western University did not have facilities for such complicated work, and in any case Macleod at Toronto was internationally-known for his expertise in carbohydrate metabolism.

The Terrors of Diabetes

The “sugar sickness”, the body’s inability to metabolize the nutrients in food, had plagued humanity for thousands of years. The Greeks named the disorder “diabetes” after their word describing a siphon or pipe-like action. People with diabetes passed large volumes of urine with a high sugar content, hence one famous description of diabetes as “the pissing evile.”

A fog of speculation about the cause of diabetes began to dissipate in 1889 when German researchers, Oskar Minkowski and Joseph von Mering, discovered that dogs whose pancreas is removed, immediately became severely diabetic. The pancreas seemed to hold the key to diabetes. It did something to control carbohydrate metabolism.

A comparatively massive research effort gradually got underway to solve the mystery of the pancreas and diabetes. Meanwhile physicians continued their struggle to treat diabetes' victims.

Therapeutic progress was excruciatingly slow. Perhaps it was a step forward to conclude that giving patients sugar supplements (to replace the sugar they were evacuating in their urine) was unhelpful. Perhaps reliance on opiates in the late stages of the disease at least dulled the pain. Still, the prognosis for those who developed diabetes at a young age (the "early onset" form of the disease) was dismal. They would suffer intense hunger and thirst, a wasting away of the flesh from lack of nourishment, ketoacidotic poisoning of the system, "air-hunger", the gradual onset of coma, and then death, all in the space of a few weeks or months after onset.

There was one important breakthrough in treatment. Physicians realized that if a body could not metabolize normal amounts of food, it should receive only as much food as it could metabolize. Under-nutrition, especially the under-feeding of carbohydrates, became state-of-the-art therapy in diabetes at the beginning of the twentieth century. Diabetics were put on special diets.

For what were called "late-onset" diabetics (whose problem is often more complex than abrupt pancreatic failure), under-nutrition could — and can — produce good results. But for young or juvenile diabetics, the diets had to be so restrictive that they usually could not maintain bodily weight. It was in fact a "starvation" therapy, offering a ghastly choice between quick death from diabetes or a few extra months, possibly a year or two, of life as the patient was deliberately starved to death. The inhabitants of diabetes wards in the age of under-nutrition became human skeletons. Few were able to maintain their diets — unless their care-givers virtually kept them prisoner.

Even after Minkowski and von Mering's breakthrough, researchers could not find the pancreatic principle that controlled metabolism. It did no good to feed diabetic patients with minced or extracted pancreas. But Eugene Opie and others did observe that so long as the islet cells in even small remnants of pancreas retained their health, diabetes did not develop. The known function of the pancreas was to excrete digestive juices into the duodenum. Did it also produce, in the islet cells, some kind of "internal secretion" directly into the bloodstream? Could that internal or endocrine secretion be isolated from other pancreatic material?

The discovery of internal secretions from ductless glands in the human body — the thyroid, the adrenal medulla, the pituitary — led to the realization in the early years of the twentieth century that organs generate chemical messengers or what in 1902 were named “hormones”. The unveiling of the body’s endocrine system became a fascinating new research frontier, with no problem as baffling as the search for a pancreatic hormone.

One researcher after another took a fling at the pancreas, all agreeing that the only proof of success would be to have something that would restore normal metabolism, in other words would relieve or treat diabetes. Detecting sugar in the urine (glycosuria) was the traditional way of diagnosing diabetes. High concentrations of sugar in the blood (hyperglycemia) were another symptom of diabetes, but until the 19-teens it was technically difficult to do blood sugar measurements.

A series of investigators, especially G.L Zuelzer in Germany and E.L. Scott in the United States, reported interesting, but very inconsistent results treating diabetic dogs and/or patients with extracts of pancreas. If Zuelzer, a Jew, had been given the kind of research support in Berlin that Banting would later receive in Toronto, or if the Great War had not disrupted his and most other European scientists’ lives, the elusive pancreatic hormone would probably have been isolated before 1920.

By the time Fred Banting began thinking about the pancreas, the search had been resumed and was becoming more focused. In 1919 Israel Kleiner of the Rockefeller Institute published an article in the *Journal of Biological Chemistry* suggesting that his pancreatic extract was almost ready to try on human diabetics (the pyrogenic or fever-causing effects of Kleiner’s and others’ extracts was the main deterrent to such testing). The distinguished Romanian physiologist, Nicolas Paulesco, also resumed his war-interrupted research, and soon had interesting results ready for publication.

John James Rickard Macleod (1876-1935) was not engaged in substantial active pancreas or diabetes research in 1920, but he was clearly the man Banting needed to see. Macleod was a distinguished graduate of Scotland’s University of Aberdeen, who had emigrated to America in 1903 to become Professor of Physiology at Western Reserve University in Cleveland, Ohio. He moved back to British territory in going to Toronto in 1918. Macleod was a prolific researcher and publisher, and had done considerable work on carbohydrate metabolism, culminating in a 1913 monograph, *Diabetes: its Pathological Physiology*. Having decided that “extreme technical difficulties” made it next to impossible to unravel the physiology of carbohydrate metabolism, Macleod wound down his own research on the subject, though naturally it maintained its interest for him.

Other researchers, especially those charged with treating people with diabetes, continued to press on. “The knowledge of diabetes is advancing rapidly enough,” wrote

the father of the under-nutrition therapy, Dr. Frederick Allen, in 1919, "that even the patient whose outlook seems darkest should take courage to remain alive in the hope of treatment that can be called curative." His desperate patients could only hope that Dr. Allen was not whistling in the dark.

The Summer of 1921

Banting almost decided against taking up the opportunity to try out his diabetes idea in Toronto. Unhappy in his practice in London (Banting thought he was failing, though his accounts show that it was growing about as quickly as could be expected), worried about a long-time romance that was drifting towards the rocks, and congenitally insecure at the best of times, Banting considered several alternatives during the winter of 1920-21. By his own account he tossed a coin to decide whether to do the research in Toronto or be a doctor on an oil exploration expedition in Canada's north. The expedition won, but Banting did not get the job. So he closed his London office at the end of the university year and went to Toronto.

True to his word, Macleod gave Banting some unused laboratory space in the physiology department, allowed him the use of a dozen or so experimental dogs, and assigned students to help him with the chemical testing his experiments would require. Macleod had hired Clark Noble and Charles Best as summer assistants; both were graduating that year in Honours Physiology and Biochemistry and intended to go on to Master's studies in physiology. Macleod asked them to work with Banting. They decided to divide the job and tossed a coin to see who would go first. While this incident,



Frederick G. Banting, ca. 1921.



Charles Best, graduation photo, 1921.

like most others involving the insulin research, later became enveloped in legend and gossip, it is fairly certain that Best won the toss.

Banting and Best did their first experiment, a pancreatectomy on a dog, on May 17, 1921. Banting had to learn the surgical techniques of depancreatization and duct-ligation; Best had to work on measuring urinary and blood sugars, along with other tests. In the early weeks of the research the pair almost came to blows over Banting's anger at Best's sloppy methods. "We understood each other much better after this encounter," Banting later wrote. The partnership became firm enough that Best was happy to stay on with Banting through the whole summer, letting Noble enjoy an extra-long holiday.

What was the plan of work? In later years, Banting and Best claimed that they had intended

from the beginning to make extracts of the pancreas of dogs whose ducts had been ligated, inject the extracts into dogs made diabetic by pancreatectomy, and hope they would find evidence of the internal secretion. Macleod, they implied, had been of no practical help to them in planning the work, indeed had soon left Toronto to spend the summer in Scotland.

Banting's original notebook and other documents from the time provide conclusive evidence that these recollections were misleading. Indeed the exact phrasing of Banting's original idea — it does not contain the word "extract" — combined with other hints in the sources, as well as his own particular expertise as a surgeon, suggests that Banting probably originally intended to do experiments in pancreatic grafting or transplanting. He hoped to take portions of duct-ligated pancreas, which had been gradually shrivelling up in the living animal for six to eight weeks, but whose islet cells Banting assumed would still be intact, and graft them into depancreatized dogs. Other researchers had been considering such experiments in an age when the rejection phenomenon was not yet well understood. Today's researchers would note simply that Banting was proposing an islet cell transplant. The point of ligating the ducts was to hope that the procedure killed off the pancreatic cells that produced the external secretion, trypsin, which Banting assumed was neutralizing the internal secretion.

Macleod and Banting discussed the research several times in May and June, and worked out a plan of attack that would involve both grafting (apparently the first resort) and the preparation of an emulsion or extract of duct-ligated pancreas. On June 14 Banting recorded in his notebook "Dr. McLeod's parting instructions":

- have dogs diabetic ...*
 (1) *intra peritoneal graft*
 (2) *subcutaneous graft*
 (3) *whole remnant intravenous injection.*
 (4) *Divided aq. 2 h intravenous*
 (5) *subcutaneous injection*

The research proved easier to talk about than to execute. One result of attempting major surgery on dogs in unsanitary and intensely uncomfortable conditions — the summer of 1921 was very hot and of course the building had no air conditioning — was the death of many of them. To replenish the supply, Banting and Best sometimes bought new dogs on the streets of Toronto, \$1-3 an animal, no questions asked. In early July the project suffered a major setback when Banting realized he had failed properly to ligate the ducts in his dogs and had, in effect, to start over again. More dogs died. Nothing was going according to plan.

At the end of July, Banting and Best had two dogs whose ducts had been tied for seven weeks, surely time enough, in their view, to destroy all the cells producing the external secretion. Banting removed the degenerated pancreas from one of the dogs (Number 391). Apparently deciding to forego a transplantation experiment, he and Best made an extract of that pancreas ("We followed your directions in preparing the extract," Best later wrote Macleod), and on the morning of July 30 injected it into a vein of a depancreatized, slightly diabetic terrier (Number 410).

Banting and Best had learned how to do blood sugar analyses on their dogs. In retrospect it cannot be determined

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Dog 410
 July 30th.
 Blood Sugar - .20
 10-15. injected 4 cc. of
 extract. (Ringer's saline cold)
 7 degenerated pancreas from
 dog - 391 -
 11-15 - Blood Sugar - .12
 2 injected 5 cc. of
 extract.
 (1. cc. extract was frozen)
 12-15 - Blood Sugar .11
 Dog drinking
 Injected 5 cc. of extract
 Vol urine 5 cc. (one neg. - Ben. qual)
 2-15. Blood Sugar - .14
 Vol urine 10 cc (5 cc per hr)
 Ben. qual neg.
 - Injected intravenously 5 cc.
 extract
 - 20 gms sugar in 200 cc water
 injected intrastomach
 - (tube felt passed into lung plus nearly
 dissolved - completely dissolved in less than 10 min)

Page from
 Banting's
 Laboratory Book
 for Dog 410.

how accurate their readings were, for they relied on a crude colorimeter, and, more significantly, probably did not test quickly enough to capture the very quick impact of intravenous injections. Dog 410 (there is no record in the original documents of the dogs having names) was not showing as high a blood sugar as a diabetic dog should have, and Banting and Best noted that it appeared to be suffering from infection. But when its blood sugar apparently declined sharply, from .20 to .12 percent, in the hour following the first injection, Banting and Best interpreted their experiment positively. "The extract seemed to have a marked effect," Best wrote to Macleod.

Further experiments on Dog 410 that day were inconclusive. The next morning Banting and Best found the terrier in a coma. It died later in the day. No autopsy was done.

The next day, August 1, two injections of extract seemed to lower the blood sugar of a severely-diabetic dog (406) and briefly revive it from coma, before it died. The third dog to receive extract, a yellow collie, number 408, was experimented on from August 3-7, receiving many injections of both control extracts and the substance Banting and Best now named "isletin" in their notebooks. The "isletin" appeared to lower its blood sugar. The collie died while the experiments were continuing. An autopsy showed widespread infection.

The results they had achieved on these three dogs excited Banting and Best, and were the basis of very enthusiastic letters they wrote to Macleod in Scotland. "I have so much to tell you," Banting's reads, "that I scarcely know where to begin." He was sure he was on to something, wanted Macleod's permission to carry on work in the lab, wanted better facilities and more help. While still waiting for Macleod's reply — in an era before air mail, let alone e-mail! — Banting, who had almost no money and had lived on a shoe-string that summer while working without pay, decided to burn his bridges and leave London.

Banting and Best began a second series of experiments before Macleod's reply arrived. Another yellow collie, Dog 92, lived without its pancreas from August 11-31 and received a number of injections of dog pancreas (and in one case cat pancreas) produced in various ways. The collie became something of a laboratory pet, whose occasional friskiness amazed and delighted the researchers; its death brought Banting to tears, at least in recollection. He never realized that he and Best made a serious error on August 17 when they did not recognize that an extract they had made from fresh whole pancreas was just as effective on the collie as extract of duct-ligated pancreas. Had they reflected on this result (it threw the fundamental hypothesis about duct-ligation and atrophication into question) Banting and Best might have speeded up the work by months.

Expanding the Research

J.J.R. Macleod was cautiously supportive of Banting and Best's work. There had to be "no possibility of mistake," he wrote Banting, urging him to "continue along the same lines," multiplying his results and controlling for several complicating variables. "It's very easy often in science to satisfy ones own self about some point but it's very hard to build up a stronghold of proof which others cannot pull down." Banting and Best were already back in the lab trying to do just this when Macleod's reply to their earlier letters arrived.

After a summer of research that was as often frustrating and discouraging as it was exciting, Banting wanted better facilities. When Macleod returned to Toronto late in September, Banting asked him for better lab and operating space, help with the animals, and a salary. By his lights Macleod had already been remarkably generous to Banting. Now he wanted to go slowly, in part because a new building was about to be opened, in part because Banting's research was still unconvincing.

Banting had a hot temper and Macleod had a well-developed sense of professorial authority. Their meeting to discuss the work and its future turned into an angry confrontation. According to Banting,

I told him that if the University of Toronto did not think that the results obtained were of sufficient importance to warrant the provision of the aforementioned requirements I would have to go someplace where they would.

His reply was, 'As far as you are concerned, I am the University of Toronto.'

Best remembered Banting saying of Macleod, "I'll show that little son of a bitch that he is *not* the University of Toronto."

In fact tempers quickly cooled, Macleod found ways of improving the facilities, and a friendly third party arranged a University of Toronto appointment for Banting as a special lecturer in Pharmacology. Macleod even found retroactive pay for Banting's summer work and Best's extra summer service.

Probably at Macleod's prodding, Banting and Best began to study the literature on their subject, jotting down notes and ideas on index cards that have survived. There was little sense in Toronto of being in a race or competition with other investigators. Had Banting and Best's scientific antennae been more highly tuned, they might have given special thought to the very impressive results that Paulesco, the Romanian, had published in the summer of 1921 just as they were starting work. Paulesco's pancreatic extracts seemed to have very promising antidiabetic prospects — but whatever attention the pair might have given to his work was nullified when Best seriously mistranslated Paulesco's French by reading the phrase "non plus" to mean "no good".

The Toronto investigators knew it was vital to show that their pancreatic extract could do more than reduce glycosuria and hyperglycemia. Others had done and were doing this. Other substances or shocks to the system could do it without restoring the metabolic function. Lowering urinary and blood sugar from time to time was not proof of discovery of the internal secretion. What should the team do next? Banting continued to be drawn to the idea of pancreas grafting. He was somehow persuaded, probably by Macleod, to stick to his extract.

Banting and Best gave the first quasi-public talk about their research to a meeting of the Physiology Department's Journal Club on November 14 (Banting's thirtieth birthday). One of the younger physiologists, Dr. N.B. Taylor, suggested afterwards that it would be a convincing demonstration of the extract's potency to show that it could prolong the life of diabetic dogs. Macleod agreed, and it was decided to proceed with a longevity experiment.

But there was very little degenerated pancreas from duct-ligated dogs at hand. Producing significant quantities of it would take several months under the best of circumstances. Banting still believed that he had to have pancreas whose trypsin-producing cells were not active. He learned from his reading that foetal pancreases have large quantities of islet cells and do not at that stage produce an external secretion. On November 16-17 he and Best tried making extract from foetal calf pancreas, obtainable in fairly large

quantity from local abattoirs. When it proved as active as the extract of duct-ligated pancreas, the supply problem seemed to be solved. The surgical procedure that had been central to Banting's original idea was abandoned.

Macleod had now abandoned much of his original scepticism. The work was entering a new stage and thoughts began to turn to the possibility that the extract might be used on human diabetics. "I may say privately that I believe we have something that may be of real value in the treatment of Diabetes," Macleod wrote to the Boston



Marjorie, Dog 33, was kept alive with injections of extract for 70 days.

diabetologist, Elliott Joslin, on November 21, "and that we are hurrying along the experiments as quickly as possible." On November 23rd Banting made the first actual injection of his extract into a human, trying it out on himself. There was no obvious reaction; no blood or other tests appear to have been done.

On December 2 the original longevity experiment ended abruptly after two weeks when the extract-receiving dog suddenly went into shock and died. A replacement dog began receiving extract. Production of the extract was now being refined, with a filtration stage and a preservative added. On December 7 Banting and Best tried using alcohol rather than Ringer's (a chilled saline) solution in making the extract. It proved a better solvent and could be more easily evaporated in preparing the final product. Banting and Best then decided to try an extract of fresh whole beef pancreas ground up in slightly acid alcohol. When it worked as effectively as the foetal pancreas, the supply problem eased still further. From then on the Toronto group made extract from fresh whole beef or pork pancreas.

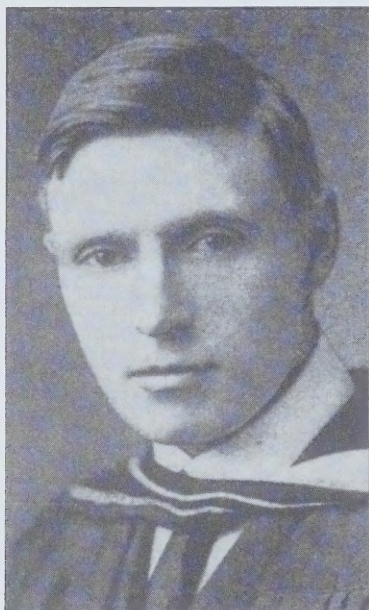
Enlarging the Team

On the occasion of one of his first meetings with Macleod, Banting was introduced to James Bertram Collip (1892-1965), an intense young scientist with a Ph.D. in biochemistry from Toronto, who had already risen to a full professorship at the University of Alberta and had considerable knowledge of both internal secretions and the preparation of tissue extracts. Collip was discussing with Macleod the prospect of working with him in Toronto, on a quite different project, as part of a sabbatical year in 1921-22. Banting wrote Collip's 1921 summer address in his original notebook, presumably as a possible resource person.

Later that autumn, after Collip came to Toronto, he got to know Banting, expressed interest in Banting and Best's work, and offered to help in any way he could. Banting had several times mentioned to Macleod the idea of enlarging the group, but Macleod encouraged him and Best to finish the original project. With the pace obviously quickening in December and Macleod having come to believe that this work could be very important indeed, it was decided to add Collip to the team. Best, who was an M.A. student at the University that year, continued to assist Banting, but was clearly, and to his discomfort, now in the shadow of the trained biochemist.

Collip began working during the second week of December, making extracts from whole beef pancreas and initially using the same methods Macleod, Banting, and Best

had developed. Collip worked in a separate lab, well away from the dog quarters. Fearing anti-vivisectionist criticism, Macleod did not like the animals being moved from one building to another. Perhaps for this reason, one of Collip's first experiments was to follow up a suggestion of Macleod's and try the extract on diabetic rabbits. Not only did it lower their blood sugar, but it also lowered that of normal rabbits, Collip discovered. Now there was a quick "rabbit test" of extract potency.



J.B. Collip, ca. 1920.

(Exactly when the group realized that the internal secretion could reduce blood sugar to a condition of severe hypoglycemic shock is not clear from the documents. It appears that Collip and/or Macleod first realized the meaning of the syndrome, but probably not until January).

As a result of consultation among the group, Collip also began experiments to test the extract's impact on the liver: would it restore the liver's ability to store glycogen, a function lost in diabetes? Collip further undertook to see if the extract reversed the ketoacidosis that developed when victims of diabetes could not metabolize fats. In preparing his own extracts, Collip also developed improvements in technique.

Banting and Best were now attempting to make larger batches of potent extract, but began having serious difficulties. Their notebooks show a consistent pattern of failure to test potent extract in the week of December 16-22, using both dogs and rabbits. Perhaps out of frustration, and apparently without telling Macleod, Banting decided to try the extract on a diabetic human. The only record of this trial is contained on one index card:

Clinical Use

Dec. 20. Phoned Joe Gilchrist —

gave him extract that we knew to be potent. — by mouth — empty stomach

Dec. 21 — no beneficial result

The extract had been administered orally because injections had occasionally caused serious shock-like reactions in animals. Banting and Best probably tested the sugar in Gilchrist's urine. They had not tested their extract orally on animals, and did not know that insulin cannot be administered orally — the test was bound to fail.

The fact of repeated failure, on a human as well as animals, could not have left Banting in a very positive mood as he and the other members of the team left Toronto after Christmas to make the first presentation of their findings at a scientific meeting. Collip, however, had achieved exciting last minute results suggesting that the extract restored glycogen-formation and abolished ketosis. This was a huge step forward from being able to attack hyperglycemia and/or glycosuria.

From Embarrassment to Triumph

On December 30, 1921, Banting delivered a paper to the American Physiological Society conference at Yale University. It was entitled "The Beneficial Influence of Certain Pancreatic Extracts on Pancreatic Diabetes", and the authors were listed as Macleod, Banting, and Best. North America's leading diabetes researchers and clinicians were in the audience.

The session did not go particularly well. "When I was called upon to present our work I became almost paralyzed," Banting remembered many years later. "I could not remember nor could I think. I had never spoken to an audience of this kind before — I was overawed. I did not present it well."

The main argument that Banting and Best offered in these early presentations (as set out in their first publication, two months later) was that their pancreatic extract "has always produced a reduction of the percentage sugar of the blood and of the sugar excreted in the urine," and therefore "we feel justified in stating that this extract contains the internal secretion of the pancreas."

The discussion at the New Haven meeting was friendly, but critical. While the audience may not have realized that Banting and Best's notebooks (and the paper they had in press) did not in fact support the claim of always being able to reduce sugar, it was certainly prepared to ask probing questions about the extent to which the Toronto work was more promising than anyone else's. Banting was undoubtedly asked about the toxicity of his extract, for example, with particular reference to the pattern of fever that Kleiner and Paulesco, among others, had reported. It would have been a difficult question to field, for Banting and Best had not taken temperature readings on their animals (the sole exception showed a dog running a high fever after injection).

Pointed questions may have been asked about Banting's early surgical techniques: was he certain that his pancreatectomies, difficult to do properly under the best of conditions, had been complete? The longevity experiment begun towards the end of

November was still on-going, but of course had had one dramatic failure. And many critical questions might have been asked about Banting's original assumptions regarding the physiology of the pancreas, both before and after ligation of its ducts.

Macleod was chairing the presentation. It was evident to him, he wrote nine months later, that Banting "had not succeeded in convincing all of his audience that the results obtained proved the presence of an internal secretion of the pancreas ... any more definitely than had those of previous investigators." Macleod joined the discussion to defend work going on in his laboratory under his supervision. He too stressed the positive effects of injections, but also may have referred to Collip's exciting findings about ketonuria and glycogen formation. The Toronto group received "little praise or congratulation, and a moderate amount of friendly but serious criticism," Elliott Joslin wrote later about that session. They had yet to prove to the world that they had a discovery.

(The greatest enthusiast in the New Haven audience was George Clowes, the research director of Eli Lilly and Company of Indianapolis. Clowes told Macleod he thought they were on to something and offered Lilly's services to develop the extract. Thinking the offer premature, Macleod was non-committal).

Banting felt particularly humiliated at his own inept public performance. He had been bailed out by Macleod, a man whom he had never liked, and who had also somewhat stolen his thunder at the Journal Club presentation in November. Banting was having much less to do in the lab now that no surgery on animals was required, and his and Best's disappointing results making and testing extract stood in sharp contrast to Collip's extremely promising work.

Despite, or perhaps because of the criticism at New Haven, the Toronto group wanted to advance to trials of the extract on human diabetics. Macleod asked Collip to prepare extract for such tests. Banting, the only practicing physician in the group, may have assumed that he would now have a new role as a clinician. These hopes were immediately dashed by the Professor of Medicine, Duncan Graham, who refused to give Banting an appointment that would allow him to work with diabetics at the University's teaching hospital, Toronto General Hospital. Banting concluded that he was deliberately being pushed out of the picture. He began muttering to people about Macleod stealing the results of his work.

Banting went to Macleod and argued that he and Best deserved the right to make the first extract that would be tested formally in the clinic (there is no evidence that Macleod ever knew about the Gilchrist trial). Although he did not yet realize how serious Banting's accusations would become, Macleod went along with the suggestion.

On January 11, 1922, a house physician at Toronto General Hospital, Ed Jeffrey,

injected fifteen cc. of extract of beef pancreas, made by Best and Banting, into the buttocks of 14-year old Leonard Thompson. Thompson was a charity case, diabetic since 1919, now reduced to less than 65 pounds on a 450 calorie diet, in severe ketoacidosis, and about to slip into a coma and die. His family consented to the trial of the extract. The extract itself was described by the chief clinician, Walter Campbell, as "a thick brown muck". On Thompson's record it was noted that he was receiving "Macleod's serum".

The trial was a failure. Leonard Thompson's blood sugar dropped from .440 to .320 percent. His 24-hour excretion of glucose fell from 91.5 grams in 3625 cc. of urine to 84 grams in 4060 cc. Tests for ketones continued strongly positive. There was no improvement in his clinical appearance, and a sterile abscess, caused by impurities in the extract, developed at the site of one of the injections. The modest effect on blood and urinary sugar was outweighed, in the clinicians' judgment, by the reaction it caused. It was decided not to give him more extract. Injections may have been given to one or two other patients with even less impressive consequences. "These results were not as encouraging as those obtained by Zuelzer," Banting wrote several years later.

On the night of January 19 Collip discovered a method by which he could remove many of the toxic contaminants from the extract. "I have had such a phenomenal break in my research ...," he wrote the President of the University of Alberta a few days later. "I finally unearthed a method of isolating the internal secretion of the pancreas in a fairly pure and seemingly stable form suitable for human administration ... I discovered a way to get the active principle free from all the 'muck' with which it appeared to be inseparably bound."

In simple terms Collip's method had involved increasing the concentration of alcohol in the mixture, which caused many contaminating proteins to be precipitated out, until he found a concentration, somewhere over 90 percent alcohol, at which the active principle itself was precipitated out. Other procedures removed enough of the remaining contaminants to make the resulting powder a marked improvement on any of the group's previous extracts.

Collip's note on preparation of insulin, ca. May 1922.

*Preparation of insulin
Collip process - Distilled
Equal parts acetone & pancreas
Put in small container added
5 cc. Con. HCl per gallon
Stir - Press out juice - filter
Concentrate filtrate on
warm air current. 500 to
1000 cc in egg tray. Leave
15 min to 45 min. Filter
immediately. Against ppt.
Alcohol to 7.4 (phenol red)
Return to clean flasks
Concentrate by decreased
temp. Add to vol of 95
alcohol - Allow to settle
Decant off alcohol layer
Filter into large vol
95% alcohol - Allow several
days for ppt. - Get the cake
in distilled water. JBC*

THE TORONTO DAILY STAR
20TH YEAR TWENTY-EIGHT PAGES TORONTO, WEDNESDAY, MARCH 22, 1922. TWO CENTS
TORONTO DOCTORS ON TRACK OF DIABETES CURE

First major press coverage of the discovery, March 22, 1922.

On January 23rd, 1922, a Monday morning, Walter Campbell began injecting Leonard Thompson with extract made by Collip. In one day his glycosuria nearly disappeared; his ketones did disappear. His blood sugar dropped from .520 to .120 — normal. He was brighter and stronger. For the first time in recorded history, an extract of pancreas had been unambiguously successful in having a distinct antidiabetic effect on a human.

The test was the best evidence yet that the Toronto extract did contain the internal secretion of the pancreas, that the Toronto adventurers had uncovered a holy grail. While it is impossible to assign an exact date for the “discovery” of insulin, January 23-24, 1922, were clearly the days on which the team knew they had a splendid triumph on their hands, if only (Macleod’s caution again) they could repeat it.

They were able to. After a few weeks’ of continuing success with Thompson and half a dozen other patients in Campbell’s clinic at Toronto General Hospital, the group submitted an article to the *Canadian Medical Association Journal*, “Pancreatic Extracts in the Treatment of Diabetes Mellitus,” by Banting, Best, Collip, Campbell and A.A. Fletcher, (by agreement the names on their publications were in alphabetical order), which announced the discovery of “a therapeutic measure of unquestionable value”. On the day the March 22 issue of the CMAJ was mailed to subscribers, the *Toronto Star* announced that Toronto doctors were “on Track of Diabetes Cure”.

What should the substance be named? The hypothesis of its production in the pancreatic cells known as the islets of Langerhans seemed firmer than ever. Banting and Best had called their original extract “isletin” in a few notebook entries. Macleod appears to have made the suggestion that it would be more appropriate in a multilingual world to revert to the Latin root. The word “insulin” is used for the first time by the Toronto group in a paper they prepared about their work for presentation to the Association of American Physicians in early May, 1922. It was later realized that two previous authors had suggested naming the internal secretion “insuline”.

On May 3, 1922, Macleod read the paper, “The Effect Produced on Diabetes by Extracts of Pancreas,” authored by Banting, Best, Collip, Campbell, Fletcher, himself,

and E.C. Noble, to the elite of American physicians, gathered in Washington, D.C. The reaction was very different from that in New Haven four months earlier. The world's leading diabetologist, Frederick Allen, proclaimed, "If, as seems to be the case, the Toronto workers have the internal secretion of the pancreas fairly free from the toxic material, they hold unquestionable priority for one of the greatest achievements of modern medicine, and no one has a right to divide the credit with them." "I think that this work marks the beginning of a new phase in the study and treatment of diabetes," said the distinguished researcher Rollin T. Woodyatt. "It would be difficult to overestimate the ultimate significance of such a step." The physicians gave the Toronto group a standing ovation.

Resurrections in Toronto

There was no time to bask in their glory. Even as kudos for the achievement began to roll in — along with innumerable requests from diabetics and their physicians for access to insulin — the Toronto team found itself in a dreadful predicament. It could not make insulin!

When Collip made his breakthrough in January, the group decided to develop it under the auspices of the University of Toronto's Connaught Anti-Toxin Laboratories, a small vaccine production facility created a few years earlier by a dynamic professor of hygiene, J.G. Fitzgerald. Collip was placed in charge of insulin manufacture and special equipment was installed.

But when he tried to make large batches of insulin Collip found they had no potency. And when he reverted to his original methods in his own lab, they did not work either. Everyone pitched in to try to rediscover the route to insulin, but it remained maddeningly elusive. From about the beginning of March, 1922 to mid-May, Toronto suffered a horrible insulin "famine". It led to the death of one patient, who could not carry on when the supply gave out (others, such as Leonard Thompson, were able to survive by reverting to their diets), and to a fundamental change of course in insulin production.

The group did, finally, regain the knack of making a few ccs. of potent insulin (the problem, as so often in early biochemical extractions, was to control all the variables in the procedures and the primitive apparatus; the scientists were like a chef trying to recreate a delicate and complex recipe in a frying pan on a wood stove). But they now saw the importance of taking legal steps to protect their priority in insulin development and the necessity of getting help.

It was decided to take out Canadian and American patents on the processes of isolating the internal secretion. These eventually were issued in the names of Banting, Best,

and Collip. The three patentees then formally transferred their rights to the Board of Governors of the University of Toronto, which would license manufacturers through a special Insulin Committee. Royalties from insulin sales would support further research.

As well, because of the production problem, the Toronto group decided to enter into a special relationship with Eli Lilly and Company of Indianapolis, whose research director, Clowes, had kept urging collaboration. At the end of May, 1922, Lilly and Toronto agreed to work together on insulin, pooling all their knowledge. In return for contributing its resources to the work, Lilly would receive an exclusive headstart in the big U.S. market (Connaught would handle Canada; the Medical Research Council in Great Britain would undertake development there; other manufacturers would be licensed in due course). His temporary appointment in Toronto having expired, Collip returned to the University of Alberta.



James Havens, ca. 1921, first American diabetic to receive insulin.

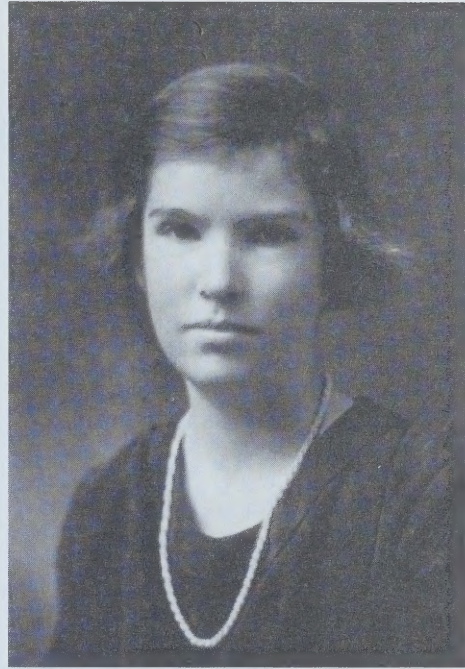
Most of the tiny batches of insulin that could be produced towards the end of May went to a single patient in the United States. The physician to a dying young man in Rochester, New York, named James Havens, had pleaded so eloquently with the Toronto team that they agreed to give Havens priority. Havens got his first injection of Toronto insulin on the evening of May 21, 1922, making him the first person treated with it in the United States. After two weeks of treatment Havens was able to get out of bed and walk.

A small handful of other starved children received insulin in Toronto in the late spring and summer of 1922. Eli Lilly, which had poured resources into the production problem, was able to begin shipping potent insulin to Toronto by early July, after which there was a gradual easing of the situation. In early August a select group of leading American clinicians began administering Lilly "Iletin" to a handful of their neediest cases.

"Diabetics swarm from all over," Banting wrote Best that July, "and think we can conjure the extract from the ground." The doctors chose to treat the most seriously ill. When Banting told the physician-uncle of five-year-old Theodore Ryder to bring the boy to Toronto in September, the reply was, "He won't be alive in September." So Ted Ryder, a 26-pound human skeleton, received his first injection in Toronto on July 10.

On that same day Banting wrote to the wife of the United States Secretary of State, Mrs. Charles Evans Hughes, denying her request for treatment of her daughter, Elizabeth. Elizabeth Hughes was fourteen years old; under the care of Dr. Frederick Allen she had been slowly starving since the onset of her diabetes in 1919. Now she was close to death from starvation.

By August the insulin shortage had eased enough — and perhaps there had been further pleading from Allen and the family — that Banting was able to change his mind and accept Elizabeth Hughes for treatment. He examined the little girl in Toronto on August 16, three days before her 15th birthday:



Elizabeth Hughes, 1923.

wt 45 lbs. height 5 ft. patient extremely emaciated, slight oedema of ankles, skin dry & scaly, hair brittle & thin, abdomen prominent, shoulders drooped, muscles extremely wasted, subcutaneous tissues almost completely absorbed. She was scarcely able to walk on account of weakness...

Elizabeth became the prize patient, not only because of her family's prominence, but also because she had sunk so low and responded so beautifully to insulin injections. Her complete patient record has survived. She was also an engaging, delightful girl, who poured out her experiences in a series of letters to her mother that are a wonderful window on a glorious time in the history of medicine:

I declare you'd think it was a fairy tale ... I look entirely different everybody says ... gaining every hour it seems to me in strength and weight ... it is truly miraculous. ... Dr. Banting considers my progress simply miraculous, none of his other patients coming near me in diet etc., and so I consider myself especially lucky. He brings all these eminent Doctors in from all over the world who come to Toronto to see for themselves the workings of this wonderful discovery, and I wish you could see the expression on their faces as they read my charts, they are so astounded in my unheard of progress

Imagine, I have to take 5cc. at a time. Isn't that awful? But it seems they have had no extract for the last few days and I suppose we were lucky to have even that poor stuff. We only have a two cc. syringe you know and so Blanche fills that and gives it to me and then unscrews it from the needle which is left sticking in to me (I feel like a pincushion) fills it again, and gives me that (am left a pincushion once more), and then have the fifth cc. It really is quite a process, and altogether takes about twenty minutes for the whole performance. My hip feels as if it would burst too, but it doesn't, although my whole

leg is numb until I walk on it a bit, then it recovers rapidly, and within an hour I would hardly know anything had been given.

I want if you can possibly find them, the links that were taken out of my little silver watch and my gold bracelet Mrs. Crozier gave me. My arm is fattening 'out so much you will be glad to hear that my watch is really becoming quite uncomfortable, so I need another link put in and I saved them for this special emergency, although I must say I didn't ever expect it to come.

The stories of the awe-inspiring impact of insulin were beginning to multiply beautifully by the autumn of 1922, first in Toronto, then rippling across North America and ultimately around the world. Banting discovered that insulin would make possible amputations on otherwise-doomed diabetic patients. Eleven-year-old Elsie Needham was brought out of diabetic coma at the Hospital for Sick Children — it seemed like bringing a person back from the dead. Jim Havens's doctor, J.R. Williams, wrote "The restoration of this patient to his present state of health is an achievement difficult to record in temperate language. Certainly few recoveries from impending death more dramatic than this have ever been witnessed by a physician." Rawle Geyelin in New York and Ralph Major in Kansas City took the "before and after" pictures that still imprint the impact of insulin in our memory.

And it was Elliott Joslin of Boston, a gentle doctor close to his Puritan heritage, who best summed up the spiritual dimension of the discovery of insulin:

By Christmas of 1922 I had witnessed so many near resurrections that I realized I was seeing enacted before my very eyes Ezekiel's vision of the valley of dry bones:

... and behold, there were very many in the open valley; and, lo, they were very dry.

And he said unto me, Son of Man, can these bones live?

And ... lo, the sinews and the flesh came upon them and the skin covered them above: but there was no breath in them.

Then said he unto me, Prophesy unto the wind, prophesy, Son of Man, and say to the wind, Thus saith the Lord God: 'Come from the four winds, O breath, and breathe upon these slain, that they may live.'

So I prophesied as he commanded me, and the breath came into them, and they lived, and stood up upon their feet, an exceeding great army.

By the end of 1922 the discovery in Indianapolis and St. Louis of the importance of adjusting the iso-electric point in insulin manufacture had ended the production problem. By the end of 1923 insulin was available across North America and in many parts of Europe as a maintenance therapy for cases of severe diabetes.

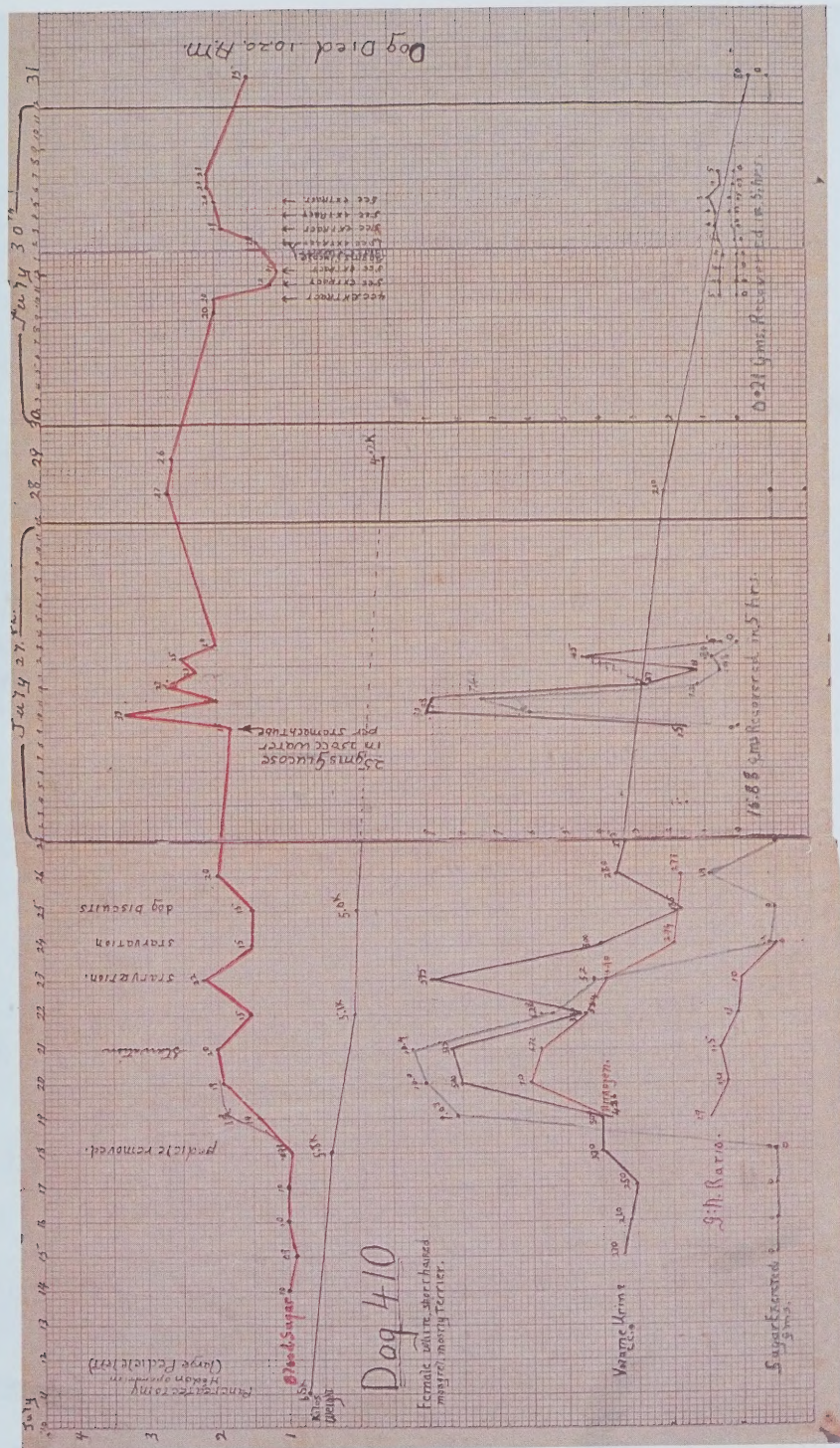


Chart of blood and urine sugars for Dog 410, July 27 - July 31, 1921.



Nobel Prize Medal for Physiology and Medicine, 1923, inscribed to F.G. Banting.



KAROLINSKA MEDIKO KIRURGISKA INSTITUTET

vilket enligt testamente,
som den 27 november 1895 upprättats av
ALFRED NOBEL,

äger att med NOBELPRIS belöna den viktigaste
upptäckt, varmed de fysiologiska och medicinska
vetenskaperna under den senaste tiden rikts, och
har denna dag beslutit att tillerkänna det år 1923
utgående priset till

FREDERICK G. BANTING
OCH
JOHN J. R. MACLEOD

för deras upptäckt av insulin.

Stockholm den 25 oktober 1923.

Carl Gustafsson *H. J. Therman* *Barndersberg*
J. J. Johansson *W. G. Gadelius* *Ellen Dalin*
Gunnar Hedén *G. M. Holmström* *Johan Almqvist*
Isaac Holmgren *Per Erik Larsson* *J. J. Jönsson*
Gösta Forsell *W. A. S. S. S. S.* *Edm. Sjögren*
Adolf Peterson *Nils Sjöström* *Ellen Sjöström*
T. H. Hämälähti *W. S. S. S. S.*

95

(1)

Wednesday Dec. 21/22
28 Talbot road.



Dear Dr. Banting
Hope you arrived safe and well.

The same day you left I gathered some nerve together and gave myself the Insulin, and doing it ever since.



I have been sugar free for the last five days, and getting about 1900 calories consisting of Pro. 60 Fat 163 Ch. 44



I am feeling great and getting Insulin only twice a day.



The Struggle for Glory

“*If every discovery* entailed as much squabbling over priority etc. as this one has it will put the job of trying to make them out of fashion,” an exasperated Macleod wrote in 1923.

The problem was not just that three of the members of the insulin team were young Canadians who had a tendency to behave under pressure like hockey players. It was not just that the pressure was almost unbearably intense, with human lives and scientific immortality clearly at stake. It was not just that Banting’s personal insecurities and scientific inadequacies predisposed him to dislike Macleod and imagine conspiracies everywhere. The problem was inherent in the discovery process itself.

Afterwards it was clear that many extracts of pancreas used by researchers, in Toronto and elsewhere, contained the internal secretion. Banting and Best’s certainly did. So did most of the extracts used by Zuelzer in Germany, Scott and Kleiner in the United States, and Paulesco in Romania. What did it mean to “discover” something you already had?

Basically, it meant supplying convincing proof that an extract contained the internal secretion. Reasonable people could disagree about the stage in a research project at which convincing proof had been supplied. Banting and Best and those who felt they were the sole discoverers of insulin, later claimed that the blood sugar tests on dog pancreas in the summer of 1921 were adequate proof of the discovery. The problem with that line of argument was (a) lack of evidence that others found Banting and Best’s work convincing; (b) the fact that other researchers, notably Paulesco and Kleiner, had previously done as much or more with their extracts as Banting and Best did. By that standard, they rather than the Canadians should be credited with the discovery. (Many Romanian scientists do believe that Paulesco was the real father of insulin and have recently been celebrating the 75th anniversary of his achievement).

To most of those involved in diabetes research at the time, proof of the value of the Toronto work came at a later stage — possibly as early as Collip’s glycogen experiment, certainly when the clinical testing on Leonard Thompson succeeded. If this was the discovery of insulin, it was clearly not simply Banting and Best’s work, but rather a collaborative process, drawing on contributions made by all four members of the team.

If Banting and Best’s extract had succeeded on Thompson on January 11, their exclusive claim might have been strengthened, but it did not. Their longevity experiment on dogs was also important in buttressing their claims, but was not a success. The first dog died; the second lived on extract until after the Thompson tests, but when killed was found not to have been completely depancreatized — it might have stayed alive without injections.

The insulin research was a process that began with a crude and unphysiological idea and evolved through increasing stages of sophistication to successful clinical trials. In retrospect, and in comparison with the situation of other researchers, the Toronto workers were able to draw on impressive resources. Banting got supervision and help from one of the world's experts in carbohydrate metabolism. He was given skilled student help, precious experimental dogs, and laboratory facilities among the best in North America. At a critical stage in the work an absolutely first-class biochemist was added to the team. Money and supplies were never a problem. Improvements in methods of doing serial blood sugars, worked out by researchers in other centres, were crucial in making the Toronto research possible.

The discovery of insulin was not the work of unfunded and unappreciated geniuses working under intolerable conditions. It was a frontal attack on the problem of the pancreas using first-class facilities, personnel, and techniques. The people of Toronto, Ontario, and Canada, had funded a great national university in the hope that just such breakthroughs might emerge. Banting did not appreciate that when he walked into Macleod's office that day in 1920 he had found a field of medical dreams.

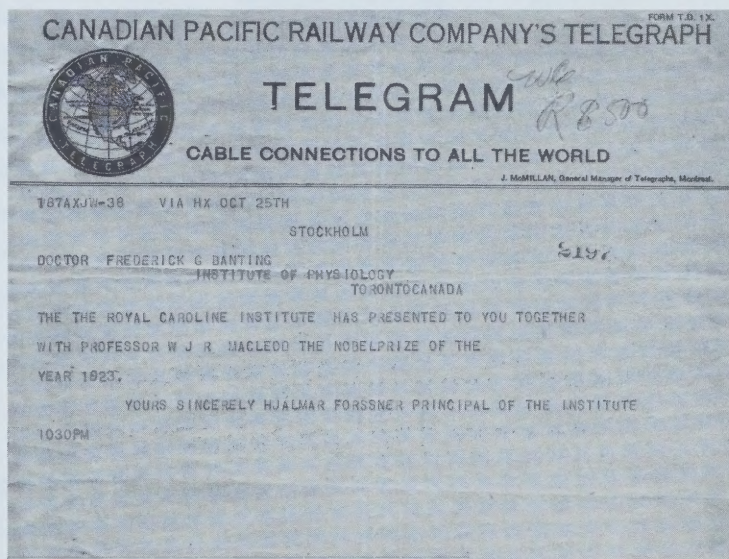
Banting was utterly determined in 1922-23 not to be upstaged by his senior colleagues. His dislike of Macleod had turned into a view by January 1922 that the physiologist, possibly in league with Collip, was taking over the work. Hence Banting's insistence on making the extract first used on Thompson. That humiliating failure, combined with news of Collip's brilliant success in purifying the extract, set the stage for the worst breakdown of the team. Banting and Collip came to blows one night in the lab when Collip refused to reveal the secret of the purification process. All members of the group had to sign a kind of "peace treaty" on January 25 to ensure that the work would go forward.

Personal relations were never fully restored. Banting and Best were not present in Washington in May, for example, for the ovation at the Association of American Physicians. While insulin progressed from triumph to triumph, a highly-political, deeply-byzantine struggle for credit, influence, and support played itself out within the University and in Toronto, Canadian, and even international medical communities. It involved Banting's struggles to emerge as the clinician who controlled insulin, his friends' determination to have him honoured as the principal discoverer of insulin, and Macleod's stubborn insistence on the importance of his and Collip's contribution to a collaborative discovery process. Officials at the University responded with caution and discretion to the pressures on them. When the Chairman of the Insulin Committee, Colonel Albert Gooderham, asked Macleod, Banting, and Best to supply him with their versions of events, he received three conflicting accounts. They were suppressed for many years.

The campaign of Banting's friends led to a decision by the government of Ontario to create for him a special Banting and Best Chair of Medical Research at the University of Toronto, the first research professorship in a Canadian university. The government of Canada, in recognition of the discovery of insulin, granted Banting a lifetime annuity of \$7,500. Everyone thought he would be in line for a title from the King if Canadians were ever allowed to receive titles again; when they were, in 1934, he received a knighthood.

Several of the distinguished scientists who were invited to nominate candidates for the 1923 Nobel Prize in Physiology and Medicine put forward the names of either Banting or Macleod. Dr. August Krogh, a Danish Nobel laureate who had visited Toronto in the autumn of 1922 (where he learned how to make insulin, leading to the very successful Danish manufacture of the product), nominated both Banting and Macleod for the Prize. Krogh argued that Banting would never have reached insulin without Macleod's contributions. He noted that Collip had made an important contribution, but did not recommend him for the Prize. The Nobel Committee of Stockholm's Karolinska Institute looked into insulin and its discovery very carefully — it was and still is almost unheard of to honour a breakthrough with a Nobel Prize so quickly — had a special debate on Macleod's role, and decided to give the 1923 Prize to Banting and Macleod.

Charles Best (1900-1978) had sometimes been the odd man out in the struggle for honours. He was by far the most junior member of the team, a handsome, relatively care-free student assistant who had found himself suddenly part of a great medical adventure. He had been involved at virtually every stage in the work, including playing an important role in the rediscovery and manufacture of insulin in Toronto, and he had given vital moral support when Banting was on the brink of collapse and was drinking heavily. Unlike Banting, Best did not have powerful friends or patrons at the University to advance his claim to an equal share in the fruits of the insulin work. Best became increasingly disgruntled when the honours were not equally divided, but had no choice except to rely on Banting's generosity.



Telegram to Banting announcing Nobel Prize, October 25, 1923.

Best was lecturing at Harvard on October 26, 1923. On hearing of the award of the Nobel Prize to Macleod and himself, Banting telegraphed to Best's host, Elliott Joslin:

At any meeting or dinner please read following. I ascribe to Best equal share in the discovery. Hurt that he is not so acknowledged by Nobel trustees. Will share with him.

MACLEOD AWARDS COLLIP HALF OF HIS NOBEL PRIZE

Total of \$40,000 Has Now
Been Divided Equally
Among Four

TEAMWORK DID IT

Varsity Professor Explains How
Credit Should Be Apportioned
for Discovery of Insulin

Dr. J. J. R. Macleod will divide his \$20,000 share of the Nobel prize for the discovery of insulin with Dr. J. B. Collip, professor in Alberta University.

To The Star to-day Dr. Macleod confirmed the fact that he had offered to make an even division of his prize money with Dr. Collip and that the latter had accepted.

This action now gives all four men who worked on the insulin experiments, Drs. Banting, Macleod, Collip and Mr. C. H. Best, an equal division of the prize money. Each gets \$10,000.

"It would be invidious and quite unnecessary to try to dissect or divide up the work on insulin among the various men who were engaged on it," said Dr. Macleod as he discussed the matter with The Star to-



DR. J. B. COLLIP
of the University of Alberta, who has been presented with \$10,000, half of the Nobel prize money awarded Dr. J. J. R. Macleod. Dr. Macleod in making this generous grant to Dr. Collip, says that it was teamwork which made insulin possible.

Macleod received the news at sea, en route to Canada from Britain. On November 7 he announced that he was dividing his share of the prize with Collip. "It would be invidious and quite unnecessary to try to dissect or divide up the work on insulin among the various men who were engaged in it," Macleod told the press. With Banting in a very sour mood about being linked forever with Macleod in scientific immortality, it was possible that enterprising reporters might have revealed the whole story of the fighting among members of the insulin team. But the best-placed reporter covering the story was a young journalist for the *Toronto Star* who hated the city and wanted to get out of it and make his name as a writer of fiction. Ernest Hemingway later was involved in his own Nobel Prize story.

The University of Toronto awarded Banting and Macleod special honorary degrees at a special dinner for its Nobel laureates, Canada's first in medicine or any other field, on November 26, 1923. One of the distinguished guest speakers, Dr. Lewellys Barker, captured the right note on remarking, "There is in insulin glory enough for all."

Afterwards

The Nobel laureates had little to do with one another. Macleod, who supervised a great deal of research on the action of insulin, left Toronto in 1928 to become Regius Professor at the University of Aberdeen, and died there in 1935.

Banting's Chair of Medical Research expanded into the Banting and Best Department of Medical Research, housed from 1930 in a medical building named the Banting Institute. Banting was more successful as a spokesman for medical research

than a laboratory worker. In 1941 he was on an official mission to study wartime research in Britain when the Hudson bomber on which he was a passenger crashed in Newfoundland. He died from his injuries.

J.B. Collip became one of the first to isolate parathyroid hormone in 1925. In 1928 he moved from the University of Alberta to McGill University; his laboratory there was on the forefront of endocrinological research in the 1930s, doing path-breaking investigations of the ovarian, gonadotrophic and adenocorticotrophic hormones. In 1947 Collip became Dean of Medicine at the University of Western Ontario, and was still engaged in research there when he died in 1965. In the mid-1920s Collip and Banting patched up their differences and became good friends.

Charles Best finished his medical degree in 1925, did a D.Sc. in England, and returned to Toronto where, at age 29, he was chosen to replace Macleod as Professor of Physiology. After Banting's death he also became Chairman of the Banting and Best Department. In 1953 the University opened the Best Institute next door to the Banting Institute. Best and his associates continued to study the properties of insulin, worked on the dietary factor choline, and were instrumental in the development of the important anti-coagulant, heparin. After Banting's death Best received many honours as the principal living discoverer of insulin. He died in 1978.

Many of the starving children who were brought back to life on insulin went on to lead normal, productive lives. Leonard Thompson, the first patient, died in 1935 of influenza and complications from his diabetes. James Havens, the Rochester boy, became a widely exhibited artist. He died of cancer in 1960 at age fifty-nine.

Elizabeth Hughes graduated from university in 1929, married, bore three children by caesarian section, and became prominent in civic affairs and volunteer work in Michigan. She died of a heart attack in 1981, in her fifty-ninth year of taking insulin.

Theodore Ryder became a professional librarian. In the 1980s he was given considerable recognition by the American Diabetes Association and other bodies as the last of the original Toronto patients. He returned to Toronto in 1990 to be present at the dedication of a new historical plaque to the discovery of insulin, the opening of a special exhibit in the Medical Sciences Building, and the naming of its auditorium in honour of J.J.R. Macleod. In July 1992 Ted Ryder became the first person to survive 70 years on insulin. He died the next spring at age seventy-six.

Both Elizabeth Hughes and Ted Ryder outlived all the physicians and scientists who had been involved in the discovery of insulin.

Sources

This account has been based on material contained in several collections of papers held in the Thomas Fisher Rare Book Library. These are the F.G. Banting Papers, the C.H. Best Papers, the J.B. Collip Papers, the W.R. Feasby Papers, and the J.J.R. Macleod Papers. I have also used the records of the Insulin Committee of the University of Toronto's Board of Governors, held in the University of Toronto Archives.

All of these collections, along with many other sources, were first drawn upon in the research that led to my book, *The Discovery of Insulin* (Toronto, McClelland & Stewart, 1982; University of Chicago Press, 1983) which is being re-released this year in a 75th anniversary edition. This book was followed by a sequel, *Banting, A Biography* (Toronto: McClelland & Stewart, 1984; 2nd edition, University of Toronto Press, 1992).

Other publications that flowed out of this project included "Banting's, Best's, and Collip's Accounts of the Discovery of Insulin", *Bulletin of the History of Medicine* (Winter, 1982-83), 56, pp.554-68; "J.J.R. Macleod and the Discovery of Insulin", *Quarterly Journal of Experimental Physiology* (1989), 74, pp.87-96; "Rewriting Medical History: Charles Best and the Banting and Best Myth", *Journal of the History of Medicine and Allied Sciences*, 48, July 1993, pp.253-274. In 1992 Alison I-Syin Li completed a very good Ph.D. thesis at the University of Toronto on "J.B. Collip and the Making of Medical Research in Canada".

Michael Bliss
Professor of History/History of Medicine

Case 1

THE BEGINNING

Ligating Islets.
Try to isolate the
internal secretion
of these to relieve
glycosuria

"Try to isolate the internal secretion ..."

F.G. Banting,
Notebook, Oct. 31, 1920

F.G. Banting. Daily accounts. 1920-21.

Account book for Banting's medical practice in London, Ont., listing patients seen, fees charged, and payments received.

Banting opened his practice on the 1st of July 1920. His first entry in his account book is dated July 29 and records a charge of \$2.00 for "baby-feeding". His practice grew slowly. In October his fees totalled \$66. Figures jotted on a prescription pad dated April 21/21 show he had received a total of \$773 in cash since setting up his practice the previous summer.

Moses Barron. "The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis." Reprint from Surgery, Gynecology and Obstetrics, Nov. 1920.

Banting read this article on the evening of October 30, 1920 as he prepared for a presentation on the pancreas he was to give the following day to students at the University of Western Ontario, where he had secured a part-time appointment as a demonstrator in surgery and anatomy.

F.G. Banting. Looseleaf notebook, 1920/21. Open at page dated Oct. 31/20. (On deposit from the Academy of Medicine, Toronto)

Ligate pancreatic ducts of dog. Keep dogs alive till acini degenerate leaving islets. Try to isolate the internal secretion of these to relieve glycosuria.

Banting jotted down this note during a sleepless night spent worrying about his finances and thinking about his lecture for the next day and the article he had just read. The idea outlined on this page inspired Banting to give up his London practice to pursue research at the University of Toronto, and eventually led to the discovery of insulin.

The notebook was donated from the estate of Dr. G.W. Ross to the Academy of Medicine, Toronto.

Dr. Clarence R. Starr, Toronto. Letter to F.G. Banting, London, Ont., Dec. 14, 1920.

Dr. Starr was chief surgeon at the Hospital for Sick Children in Toronto. Banting admired and respected Starr, having worked under him at Granville Canadian Special Hospital in

England during the war and later at the Hospital for Sick Children. After Banting had discussed his idea for diabetes research with J.J.R. Macleod, head of the Physiology Department at the University of Toronto, he consulted Dr. Starr as to whether he should give up his London practice.

In this letter Starr advises Banting against giving up his practice, telling him that Macleod viewed his idea as "very problematical". The letter concludes:

I feel pretty strongly myself that your wise plan is for you to stick to your post and keep on with your surgical work there. I feel you have a great future there if you stick right with it.

J.J.R. Macleod, Dept. of Physiology, University of Toronto. Letter to F.G. Banting, London, Ont., March 11, 1921.

I shall be glad to have you come up here on May 15th, as you suggest, to see what you can do with the problem of Pancreatic Diabetes, which we spoke about.

Despite initial discouragement from both Macleod and Starr, Banting had decided to pursue his research at the University of Toronto although he postponed his decision to close down his practice.

Photograph of J.J.R. Macleod, ca. 1921.

Photograph of F.G. Banting, ca. 1921.

Graduation photograph of Charles Best, spring 1921.

Best received his B.A. in Honours Physiology and Biochemistry in the spring of 1921.

Photograph of Charles Best and Clark Noble. ca. 1920 or 1921.

Macleod had hired Best and his classmate, Clark Noble, as summer assistants in the Department of Physiology. Both planned to take their Masters in Physiology the following year. When Macleod asked them to work with Banting they tossed a coin to see who would go first. Best won the toss and, with Noble's agreement, stayed with the work all summer. Clark Noble joined the expanded research team later in the fall.

Photograph of the Medical Building, University of Toronto, in the 1920s.

This building was demolished when the present Medical Sciences Building was built.

F.G. Banting. Page dated May 17 from his Looseleaf notebook, 1920/21.

"Exp. 1. Dog 385. Brown Spaniel female ..."

Notes on the first pancreatectomy carried out by Banting, assisted by Best. Macleod was present at this first operation to advise on procedure.

F.G. Banting. Page dated June 14 from his Looseleaf notebook, 1920/21.

A list entitled "Dr. McLeod's parting instructions". Macleod had been discussing the experiments with Banting throughout the past month, as other entries in the notebook indicate, but in mid June he left Toronto to spend the summer in Paisley, Scotland. He returned to the University in mid September.

F.G. Banting. Page dated July 30 in Laboratory notebook [1], 1921.

Notes on Banting and Best's first experiment using pancreatic extract on a diabetic dog. Dog 410, previously rendered diabetic through a pancreatectomy, was injected with the extract. In an hour the dog's blood sugar had fallen from .20 to .12, convincing both researchers that they were on the right track.

Chart showing blood sugar, urine volume and urine sugar for Dog 410. July 30-31, 1921.

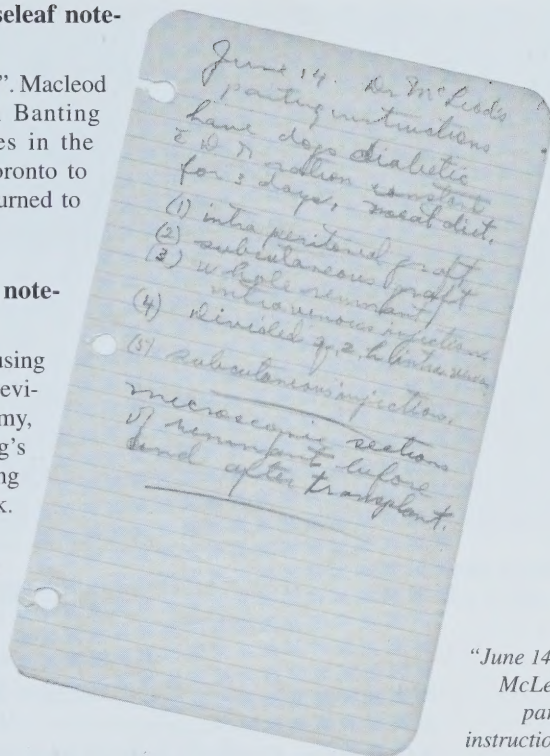
The drop in blood sugar after injections of extract is clearly marked. Charts like this one were part of the experimental records kept for each dog.

F.G. Banting. Page dated Aug. 1 from Laboratory notebook [1], 1921.

Notes on the second trial of pancreatic extract. Dog 406, already in a coma, received two injections of extract. It revived briefly, was able to stand and walk, and its blood sugar fell from .5 to .37 in two hours. The dog then relapsed into coma again and died.

F.G. Banting. Pages dated Aug. 6-7 from Laboratory notebook [1], 1921.

Notes on the third experiment using pancreatic extract. Dog 408 was depancreatized on Aug. 3. Injections of the pancreatic extract — for the first time referred to in the notes as "isletin" — caused its blood sugar to drop from .43 to .21 during the night of Aug. 6-7.



"June 14, Dr. McLeod's parting instructions."

Case 2

THE SUMMER OF 1921

*the night and to-day until two.
we got fine results - The
prize dog died to-day at about*

"We got fine results"

*C.H. Best, Letter to
Margaret Mahon, Aug. 8/21.*

C.H. Best. Letter to his fiancée, Margaret Mahon, Coniston, Ont., Aug. 8/21. (Lent by Dr. Henry Best)

Best enthusiastically describes the successful experiments of the previous week.

I went back to the Lab at eleven P.M. and we worked all through the night and to-day until two. We got fine results.

Photograph of C.H. Best and Margaret Mahon, 1921. (Lent by Dr. Henry Best)

F.G. Banting. Draft of a letter to J.J.R. Macleod, Paisley, Scotland, Aug. 9/21.

Banting reports the results of his recent experiments with confidence and excitement.

I have so much to tell you and ask you about that I scarcely know where to begin ... At present I can honestly state my opinion that ... the extract invariably causes a decrease in the percentage of blood sugar & in the excretion of sugar in diabetic dogs.

C.H. Best. Draft of a letter to J.J.R. Macleod, Paisley, Scotland, Aug. 9/21.

Best's letter begins on a more qualified note:

We have delayed writing you because, until recently, we have not been able to secure any significant results. Infection has been our great trouble ... Our most convincing experiment is the record of Dog 408.

Chart for Dog 92, August 11-24, 1921.

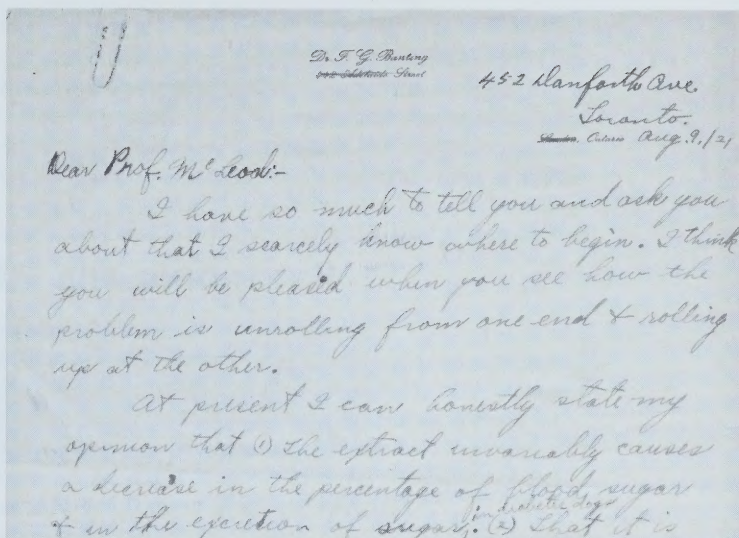
Banting and Best began a comparative experiment on August 11, depancreatizing two dogs. The control dog, Dog 409, received no extract and died four days later. Dog 92 received regular injections of pancreatic extract and survived for twenty days, from Aug. 11 to Aug. 31. The chart for Dog 92 shows the variations in blood sugar resulting from the administration of extracts prepared in a variety of ways and of varying strengths.

C.H. Best. Letter to Margaret Mahon, Coniston, Ont., Aug. 11, 1921. (Lent by Dr. Henry Best)

We are spending to-night in the Physiology department; have done five operations to-day and due to work day and night for several days.

F.G. Banting. Page dated Aug. 14, 1921 in Laboratory book [2].

These notes document an experiment to see whether an overdose of the extract would cause the blood sugar to fall below normal (.09). The dog was given 20 cc. of extract and its blood sugar fell from .37 to .066 in just over an hour.



F.G. Banting, Draft of letter to J.J.R. Macleod, Aug. 9/21.

F.G. Banting. Pages dated Aug. 20-21 from Laboratory book [2].

These notes show dramatic reductions in Dog 92's blood sugar occurring after injections of a powerful new extract were given. The dog, which on the evening of August 20 was weak and sluggish, had regained much of its strength by the following afternoon.

*Her spirits are excellent she gets up & wags tail on our approach ... 2 pm.
Blood sugar: — Dog jumped out of cage to floor about 2 1/2 feet & did not fall
— she is in excellent spirits.*

J.J.R. Macleod, Paisley, Scotland. Letter to F.G. Banting, Aug. 23, 1921.

Macleod's reply to Banting's and Best's letters was cautious.

The results of your experiments are certainly very encouraging but in order that there may be no possibility of mistake I would suggest that you continue along the same lines without at the present taking up any of the problems which you suggest in your letter ... I would say your results on Dog 408 were not absolutely convincing ... your results are definitely positive, but it is not absolutely certain.

He did, however, promise to continue his support for the research.

Regarding your plans, I am glad to see that you are to stay in Toronto & you may rest assured that I will do all in my power to help you.

The letter closes with a word of commendation for Best.

Tell Best that I am very pleased with the way he appears to be doing his work & give him this letter to read so that he may meet my criticisms by using data on other dogs.

Photograph of room 221 in the old Medical Building, ca. 1921. (Lent by the University of Toronto Archives. A65-0004/4.23)

It was in this laboratory that Banting and Best carried out many of their experiments in the summer of 1921.

Case 3

EXPANDING THE RESEARCH

...our findings at the meeting of the Physiological Society at New
which time we expect to be in a position to come to a definite
sion. I may say privately that I believe we have something that
of real value in the treatment of Diabetes and that we are hur-
ing the experiments as quickly as possible. With regards, I am

"I believe we have something that may be of real value"

J.J.R. Macleod, Letter to
E.P. Joslin, Nov. 21, 1921.

J.J.R. Macleod. Letter to Sir Robert Falconer, President, University of Toronto, Sept. 30, 1921. (Lent by the University of Toronto Archives. Falconer Papers. A67-0007/72)

Macleod recommends that Charles Best and F.G. Banting each receive \$150 from the Department of Physiology's research funds for their research during the summer.

C.H. Best. Note on Paulesco's article on pancreatic extract. [1921]

This card is from an index file which Banting and Best compiled during the fall of 1921 as they read through the published literature on diabetes. Best's note summarizes an article by the Romanian scientist, Nicolas Paulesco, which had been published in French in July 1921.

Paulesco reported that he had obtained excellent results using pancreatic extract in experiments which were similar to those of Banting and Best. The note, however, contains a misquotation from Paulesco's article which obscured its significance. The phrase "non bon" was substituted by mistake for Paulesco's original phrase "non plus".

F.G. Banting. Note card. Oct. 1921.

These notes show Banting already anticipating using his extract to help diabetics. His note in part reads "... a human might be improved by a 'course of treatment'".

Notice announcing a meeting of the University of Toronto's Physiological Journal Club on Nov. 14, 1921. (Lent by Dr. Henry Best)

At this meeting Banting and Best gave the first public presentation of their research. Macleod introduced the speakers. Banting then described the research while Best showed slides of the charts illustrating their experiments.

F.G. Banting. Pages dated Nov. 16-18, 1921 from his Laboratory notebook [3].

These pages record the first use of extract made from foetal calf pancreas obtained from a Toronto slaughterhouse. Dog 27 received the extract on Nov. 18 and became sugar free for 24 hours. The discovery that an effective extract could be made from readily obtainable foetal calf pancreas was an important step forward in the research since it meant that the researchers no longer had to carry out pancreatectomies on experimental dogs to obtain the extract.

The entry for Nov. 18 also records the pancreatectomy on Dog 33, later to become the subject of a longevity experiment.

Photograph of Dog 33. [Dec. 1921]

This dog, later referred to as "Marjorie", became the subject of the second longevity experiment and was kept alive for seventy days, from Nov. 18, 1921 to January 27, 1922, receiving daily injections of extract. The subsequent autopsy showed, however, that the dog still had a small nodule of pancreatic tissue remaining in her duodenum. Although it is unlikely that this remnant alone enabled her to survive, the experiment remained inconclusive.

Chart showing blood sugar readings for Dog 33, Nov. 18-25, 1921.

Elliott P. Joslin. Letter to J.J.R. Macleod, Nov. 19, 1921. (Carbon copy)

Dr. Joslin, one of the foremost specialists in the treatment of diabetes, writes from Boston to inquire about Macleod's research on pancreatic extract.

Naturally if there is a grain of hopefulness in these experiments which I can give to patients ... it would afford much comfort, not only to them, but to me as well, because I see so many pathetic cases.

J.J.R. Macleod. Letter to Dr. Elliott P. Joslin, Nov. 21, 1921.

Macleod's reply reads in part:

It is true that we have been doing work on the influence of Pancreatic extracts, which has yeilded [sic] most encouraging results ... Dr. Banting and Mr. Best, who have been doing this work, are to report their findings at the meeting of the Physiological Society at New Haven ... I believe we have something that may be of real value in the treatment of Diabetes and that we are hurrying along the experiments as quickly as possible.

F.G. Banting. Page dated Nov. 23, 1921 from his Laboratory notebook [3].

Banting's entry records the first trial of the extract on a human being — himself.

10.00 AM. One of us (F.G.B) had 1 1/2 cc Berk. ext. subcut. no reaction.

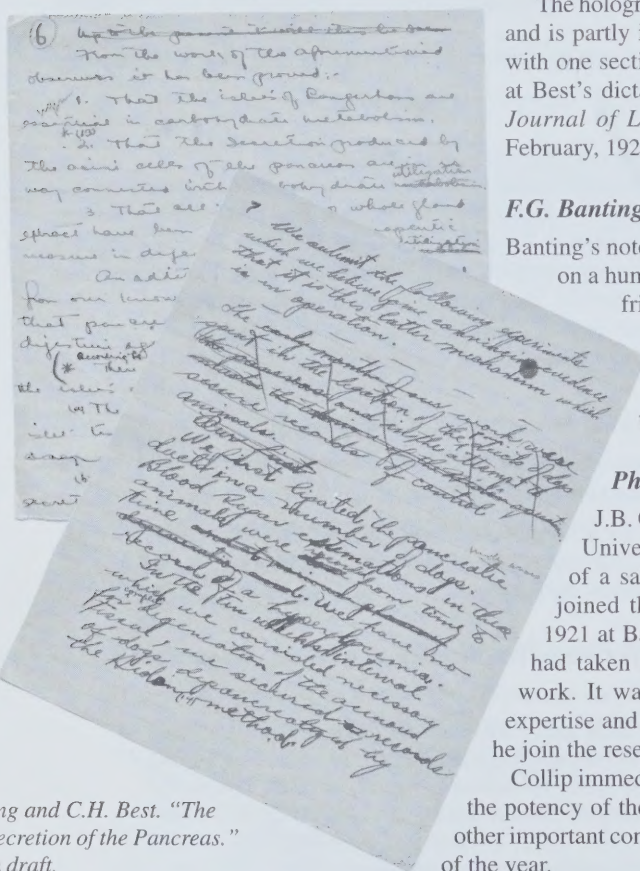
F.G. Banting. Page dated Dec. 7, 1921 from his Laboratory notebook [3].

The entry records the first use of alcohol instead of Ringer's solution in the preparation of the pancreatic extract.

F.G. Banting and C.H. Best. "The Internal Secretion of the Pancreas." Holograph draft. Nov. 1921. (Lent by Dr. Henry Best)

F.G. Banting and C.H. Best. "The Internal Secretion of the Pancreas." Reprinted from the Journal of Laboratory and Clinical Medicine, vol. 7, no. 5 (Feb. 1922).

This was the first formal paper published by Banting and Best on their research. It is a revision and expansion of the short address given to the Physiological Journal Club on Nov. 14, 1921.



F.G. Banting and C.H. Best. "The Internal Secretion of the Pancreas." Holograph draft.

The holograph draft was written in November 1921 and is partly in Banting's hand and partly in Best's, with one section in Margaret Mahon's hand, written at Best's dictation. The paper was published in the *Journal of Laboratory and Clinical Medicine* in February, 1922.

F.G. Banting. Note card dated Dec. 20-21, 1921.

Banting's notes on the first trial of pancreatic extract on a human diabetic. Dr. Joseph Gilchrist was a friend and former classmate of Banting's.

He had become diabetic shortly after graduation in 1917. Since the extract was administered orally, not injected, there was "no beneficial result".

Photograph of J.B. Collip. ca. 1920.

J.B. Collip, Professor of Biochemistry at the University of Alberta, who was spending part of a sabbatical at the University of Toronto, joined the research group in early December 1921 at Banting's request. During the fall Collip had taken a keen interest in Banting and Best's work. It was Banting who, recognizing Collip's expertise and experience, suggested to Macleod that he join the research team.

Collip immediately developed procedures for testing the potency of the extract on rabbits and began to make other important contributions to the research before the end of the year.

Case 4

FIRST CLINICAL TRIALS

*Since I've been waiting you
I have had such a phenomenal
break in my research that
I must tell you soon*

"I have had such a phenomenal break in my research"

J.B. Collip, Letter to
Dr. H.M. Tory, Jan. 25/22

J.B. Collip. Letter to Dr. H.M. Tory, President, University of Alberta, Edmonton, Jan. 25, 1922. (Reproduced from the original in the H.M. Tory Papers in the University of Alberta Archives. 68-9-144)

In this letter Collip describes his recent breakthrough in refining the extract and removing the toxic contaminants.

I have had such a phenomenal break in my research ... Last Thursday Jan. 19th I finally unearthed a method of isolating the internal secretion of the pancreas in a fairly pure and seemingly stable form suitable for human administration ...

Toronto General Hospital. Patient records for Leonard Thompson. Jan. 1921. (Reproduced from the originals held by The Toronto Hospital)

These records document the first trials of pancreatic extract on a diabetic patient. Leonard Thompson had been admitted to Toronto General Hospital on Dec. 2, 1921, suffering from acute diabetes. By early January he was close to death.

The entries record the first test of extract on Leonard Thompson on January 11 and the dramatically successful second test on January 23.

The extract used in the first test had been prepared by Banting and Best (but is called Macleod's serum in the notes). Although it caused a slight lowering of blood sugar, it contained contaminants which caused an abscess to develop at the site of the injection. The extract used in the second test had been prepared by Collip and appeared to be more potent and purified. After the second series of injections Thompson's blood sugar dropped to normal in one day and his condition showed an immediate improvement.

The extracts were administered under the direction of W.R. Campbell, chief clinician.



Leonard Thompson in later life.

Photograph of Leonard Thompson in later life.

Leonard Thompson lived for thirteen years on insulin. He died in 1935, at the age of twenty-seven, of broncho-pneumonia and complications from his diabetes.

Memorandum in reference to the co-operation of the Connaught Antitoxin Laboratories in the researches of Dr. Banting, Mr. Best and Dr. Collip under the general direction of Professor J.J.R. Macleod to obtain an extract of pancreas having a specific effect on the blood sugar concentration. Jan. 25, 1922. (Lent by the University of Toronto Archives. Insulin Committee Records. A82-0001/9/3)

An agreement whereby the Connaught Antitoxin Laboratories will collaborate with Macleod's research team in the development and production of extract, providing laboratory space, technical assistants, and assuming expenses up to \$5000. In return the research team agrees that no steps will be taken to patent the process of obtaining the extract without a joint conference between all four members and the head of the Connaught Antitoxin Laboratories, J.G. Fitzgerald. The agreement is signed by Macleod, Best, Collip and Banting.

This formal agreement was intended to promote better relations between those on the research team and allay fears that results were not being shared freely.

Notice for a meeting held Feb. 7, 1922, at the Academy of Medicine in Toronto. (Reproduction of original)

F.G. Banting and C.H. Best. "The effect of Pancreatic Extracts on blood sugar and urinary sugar on experimental diabetes." Feb. 1922.

Manuscript draft in Banting's hand of the paper read at the Academy of Medicine, Feb. 7, 1922. The lecture was published under the title of "The Internal Secretion of the Pancreas" in the *Transactions of the Academy of Medicine, Toronto*, vol. 3 (1920-22).

F.G. Banting and C.H. Best. "Pancreatic Extracts." [Feb. 1922] Typescript.

F.G. Banting and C.H. Best. "Pancreatic Extracts." Reprinted from the Journal of Laboratory and Clinical Medicine, vol. 7, no. 8 (May 1922).

The second major paper by Banting and Best. The paper outlines their experiments from mid-November to the end of January and the conclusion of their longevity study with Dog 33. Written in February, it was published in May 1922.

C.H. Best. Letter to his father, Dr. Herbert Huestis Best, West Pembroke, Maine, Feb. 12, 1921 [i.e. 1922] (Lent by Dr. Henry Best)

Best explains that he and Banting are now testing their extract on "a doctor who is a diabetic". This doctor was Joseph Gilchrist who was later to refer to himself as a "human rabbit". Gilchrist later took charge of the diabetic clinic set up at Christie St. Hospital. Best also refers to the hectic pace of work during the previous summer.

Our notes show that we worked fourteen nights and 31 days in August. And at one time five days and nights without more than one hour's sleep a night. We don't work thru the night now but the days are from 9 am to 11 pm quite often.

F.G. Banting, C.H. Best, J.B. Collip, W.R. Campbell, and A.A. Fletcher. "Pancreatic Extracts in the Treatment of Diabetes Mellitus. Preliminary Report." Reprinted from Canadian Medical Association Journal, 2, 141 (Mar. 1922). (On deposit from the Academy of Medicine)

This paper, which describes Leonard Thompson's case in detail, constitutes the first official announcement that an extract had been developed which alleviated the symptoms of diabetes in human beings.

Newspaper clipping: "Toronto Doctors on Track of Diabetes Cure." Toronto Daily Star, Mar. 22, 1922.

Newspaper clipping: "Have They Robbed Diabetes of its Terrors?" Toronto Daily Star, Mar. 22, 1922.

The first major press coverage of the discovery, timed to coincide with the publication of the research team's article in the *Canadian Medical Association Journal*. Both articles were written by *Star* reporter Roy Greenaway. Ironically, by the time these articles were published the research group was having difficulty producing a usable extract.

Photographs of C.H. Best and F.G. Banting with one of the experimental dogs on the roof of the Medical Building. Dated in Banting's hand "about Ap. 1922".

These photographs, frequently reproduced in articles about the discovery of insulin, are usually dated to the summer of 1921. Banting himself, however, has supplied the later date on a copy of one of the photographs formerly pasted into his scrapbook.

F.G. Banting, C.H. Best, J.B. Collip, W.R. Campbell, A.A. Fletcher, J.J.R. Macleod, and E.C. Noble. "The Effect Produced on Diabetes by the Extracts of Pancreas." Reprinted from the Transactions of the Association of American Physicians, 1922.

J.J.R. Macleod, as spokesman for the whole research group, delivered this paper on May 3, 1922 to the annual meeting of the Association of American Physicians in Washington, D.C. The evidence outlined here convinced the audience of medical specialists that an effective treatment for diabetes had indeed been discovered. This was the first widely publicized announcement of the discovery and also the first time the extract had been referred to publicly as "insulin".

Banting and Best with one of the experimental dogs on the roof of the Medical Building.



Case 5

THE MANUFACTURE OF INSULIN

POSTED Indianapolis Ind July 12 1922
TO Dr J.J.R. MacLeod Marine Biological Station
St Andrews N.B.
Our small scale method is now
giving good results and we hope
to maintain a small but steady
production by this means while in-
stalling a larger plant stat Banting

“Our small scale method is now giving good results”

G.H.A. Clowes, Telegram to
J.J.R. Macleod, July 13, 1922.

F.G. Banting, C.H. Best, J.B. Collip, J.J.R. Macleod, and J.G. Fitzgerald. Copy of a letter to Sir Robert Falconer, President, University of Toronto. April 12, 1922.

The members of the research group wrote to President Falconer to propose taking out a patent on the process for making pancreatic extract under the names of Best and Collip, “the two lay members who have been mainly responsible for the detailed work on the preparation”. The patent would then be turned over to the University. Such an action would safeguard the preparation process from any attempt to patent it for private gain.

F.G. Banting, C.H. Best and J.B. Collip. Assignment of the patent for the preparation of the extract to the University of Toronto’s Board of Governors for the sum of one dollar. Jan. 1, 1923.

Dr. John Howland, Johns Hopkins Hospital, Baltimore. Letter to J.J.R. Macleod, May 13, 1922. (Lent by the University of Toronto Archives. Insulin Committee Records. A82-0001/43/7)

One of the many pleas for insulin that Macleod was to receive in the weeks following his announcement of its discovery at the May meeting of the Association of American Physicians in Washington.

G.H.A. Clowes, Lilly Research Laboratories, Indianapolis. Letter to J.J.R. Macleod, May 11, 1922. (Lent by Connaught Laboratories Archives)

Clowes, as Research Director at the Eli Lilly Company’s Research Laboratories, proposes a collaboration between the Lilly and Connaught Laboratories in developing a method for large scale production of insulin.

Since hearing your paper in Washington ... I am more than ever convinced of the necessity of starting work on the problem of large scale production of this product with as little delay as possible. Your paper ... has created an extraordinary amount of interest throughout the country and I have already received inquiries for the product.

Clowes had approached Macleod with an offer of collaboration shortly after hearing him

speak at the December meeting of the American Physiological Society. At that time Macleod had refused the offer as premature. This time he felt it would be wise to accept.

G.H.A. Clowes, Indianapolis. Telegram to J.R. Macleod. May 25, 1923. (Lent by Connaught Laboratories Archives)

*... Our people greatly appreciate the consideration you have shown us ...
Mr. Lilly and the officers of the Company join me in pledging whole hearted
cooperation with a view of making the product available for the medical
profession at the earliest possible date and in the largest possible amount.*

Copy of Indenture between the Governors of the University of Toronto and the Eli Lilly Company of Indianapolis, May 30, 1922.

This document gave the Eli Lilly Company exclusive rights to the manufacture of insulin for the United States and Central and South America. The Connaught and Lilly Laboratories promised to share their knowledge and work together on the production problems.

J.B. Collip. Note headed: "To prepare Insulin. Collip Process. Dec. 22/21."

The note captures some of the urgency and excitement of the research carried out at this time. Aside from this jotted down procedure, no other laboratory notes by Collip relating to his Toronto research have survived.

The date appears to have been added later, but although it is in Collip's hand, it cannot be correct. The extract was not referred to as insulin in December 1921. The note was probably written in the spring of 1922 when Collip made a trip down to the Lilly Laboratories in Indianapolis. A note on the back refers to Eli Lilly Co. paying travelling expenses.

F.G. Banting, C.H. Best, J.B. Collip, and J.J.R. Macleod. "The Preparation of Pancreatic Extracts containing Insulin." Reprinted from the Transactions of the Royal Society of Canada, 1922.

One of five papers by members of the research group presented at the May meeting of the Royal Society of Canada. Two separate methods of preparation are outlined, the earlier method used by Banting and Best and the one used by Collip for the first successful clinical trials.

G.H.A. Clowes, Indianapolis. Telegram to J.J.R. Macleod, Marine Biological Station, St. Andrews, N.B., July 13 [1922] (Lent by Connaught Laboratories Archives)

*Our small scale method is now giving good results and we hope to maintain
a small but steady production by this means while installing a larger plant.
Banting has tested our product on human cases and found it satisfactory ...*

J.K. Lilly, Indianapolis. Letter to F.G. Banting, July 26, 1922.

J.K. Lilly, the President of the Eli Lilly Company, assures Banting that he can count on receiving 500 units of "Ile'tin" from the Lilly Laboratories every week from now on.

A few days earlier Banting and D.A. Scott, from Connaught, had visited the Lilly Laboratories to see the operation and to beg some additional extract for Banting's own patients in Toronto. The Connaught Laboratories had not been able to produce satisfactory extract in sufficient quantities to meet his needs. J.K. Lilly had been able to arrange for Banting to take back to Toronto an additional 150 cc.

F.G. Banting. Letter to C.H. Best, West Pembroke, Maine, July 27 [1922] (Lent by Dr. Henry Best)

Banting writes that he had seen a vacuum still in operation at the Lilly Laboratories and realized that similar equipment would enable Connaught to improve the quality of its insulin. He hopes to raise the money to purchase the equipment himself.

There is no doubt in my mind that the vacuum system is the one we must adopt sooner or later ... I am going to New York Sund [sic] night to get some money if possible. The lab. have not turned out one cc. of really unobjectionable stuff since you left.

F.G. Banting. Draft of a letter to Sir Robert Falconer, President, University of Toronto. Aug. 5, 1922.

Mr. Bacon of New York is very much interested in the work on Diabetes being carried out in this University. He has offered the sum of ten thousand dollars (\$10,000) through Dr. Geylin [sic], his physician, in order that the work may be carried out more rapidly.

Banting travelled to New York to see Dr. H. Rawle Geyelin, an American diabetic specialist who had visited Toronto earlier in the year and had indicated he might be able to help if Banting needed money for his research. Dr. Geyelin contacted one of his patients who was the father of a diabetic child and a large donation was immediately forthcoming.

University of Toronto, Special Advisory Committee on Diabetes. Minutes. Aug. 17, 1922. (Lent by the University of Toronto Archives. Insulin Committee Records. A82-0001/44/1)

Minutes for one of the early meetings of an Advisory Committee which had been set up to handle the distribution of insulin for the University. The Committee was chaired by Colonel Albert Gooderham. Banting, Best, Macleod, and R.D. Defries, Acting Director of the Connaught Laboratories, were all members.

The minutes record the transfer to the Connaught Laboratories of the recently received donation of \$10,000 "in accordance with the wishes of the donor". The minutes include a reference to the establishment of a new diabetic clinic at the Toronto General Hospital.

Dr. Frederick M. Allen, The Physiatric Institute, Morristown, N.J. Letter to F.G. Banting, Aug. 16, 1922.

I take pleasure in informing you that our first results with your pancreatic extract have been marvellously good. We have cleared up both sugar and acetone in some of the most hopelessly severe cases of diabetes I have ever seen.

Dr. Allen was regarded as the leading diabetic researcher in the United States. He had pioneered the "starvation treatment", and in 1919 he had set up a private hospital primarily for treating diabetics and for conducting research into the disease.

Case 6

EARLY PATIENTS

SEE ME. I AM A FAT
BOY NOW AND I FEEL

"I am a fat boy now"

Teddy Ryder, Letter to F.G. Banting, [1923]

Photograph of James Havens, the first American diabetic to receive insulin, ca. 1921.

In May 1921 twenty-two year old Jim Havens was in the last stages of diabetes. He had been diagnosed as diabetic at age fifteen and for several years his disease had been partially controlled by a rigid diet. By the spring of 1921, however, he weighed less than seventy-four pounds, and was too weak to sit up in bed.

In mid May, Havens's doctor, J. S. Williams, came to Toronto to make a personal appeal to Dr. Macleod for a chance to try out the new extract on his patient. Macleod and Banting agreed and on May 21 Jim Havens received his first injection. The initial injections appeared to have no effect but after Banting himself travelled to Rochester to examine Havens and adjust the dosage, his condition improved substantially. In two weeks he had regained enough strength to walk about the house.

Connaught Antitoxin Laboratories, University of Toronto. Invoice for insulin supplied to Dr. Banting, June 20, 1922.

A total of 141 cc. were supplied at a cost of \$1.00 per cc. Most of this supply was sent to Jim Havens in Rochester.

John S. Williams, Rochester, N.Y. Letter to F.G. Banting, July 11, 1922.

The letter describes Havens's difficulties tolerating the insulin that the Connaught Laboratories was supplying.

We have had a lot of trouble with Jim Havens. The injections became so painful that I had to discontinue them for a few days. Yesterday I thought that he would die on me. He appeared to be heading for coma. To avert it I injected 8 c.c. of the extract into the buttocks. He immediately complained of a sensation all over his body as though he had been poisoned, and of a profound burning in the stomach ... intensely itching wheels broke out on his body. I thought he would die but he came out of it all right.

James Havens, Rochester, N.Y. Letter to F.G. Banting, Aug. 12, 1922.

Jim Havens's father, James Havens senior, vice-president of Eastman Kodak, writes to thank Banting for arranging for his son to receive insulin from Lilly Laboratories.

Jim is very patient with it all. I cannot say that he is hopeful but he is bound to do his best as he has been during all these seven and one-half years.

Jim Havens, Rochester, N.Y. Letter to F.G. Banting, Dec. 11, 1922.

Gradually over the next few months Jim Havens did improve as the insulin he received improved in quality. His strength increased with his weight and his former optimism returned.

A week ago last Thursday ... marked an historical event as I then tasted my first Egg on Toast. Egg on Toast is my idea of the only food necessary in heaven ... Well, Thanksgiving has recently become a great institution over here; you ought to celebrate it there. It makes a fellow think a lot of great sentimental stuff about his good fortune and how lucky he is ...

Photograph of Jim Havens with one of his children. (Lent by Dr. Henry Best)

Jim Havens continued to thrive on insulin. He became a well known artist and illustrator in the United States. He also married and became the father of two children. He lived until the age of sixty when he died of cancer.

Dr. Morton Ryder, New York City. Letter to F.G. Banting, June 15, 1922.

Dr. Ryder asks Banting whether he would be able to treat his little nephew, Teddy Ryder, if he was brought to Toronto in July.

We must not delay if the boy's life is to be saved ... He is now, as you will judge from the weight (26 lbs.), very considerably emaciated. He walks about the house tho to look at his legs one would suppose him unable even to stand.



F.G. Banting. Letter to Dr. Morton Ryder, Carmel, N.Y., Sept. 11, 1922.

I am pleased to be able to report to you that Teddy has been progressing very satisfactorily ... on the whole he has gained very considerably in strength and weight.

Photographs of Teddy Ryder, July 10, 1922 and July 10, 1923. (Originals lent by Dr. Henry Best)

The first photograph shows six year old Teddy Ryder when he first arrived in Toronto. He weighed twenty-seven pounds. The second photograph shows him a year later, a healthy looking seven year old weighing forty-five pounds.

Teddy Ryder. Letter to F.G. Banting. Undated, probably early 1923.

I wish you could come to see me. I am a fat boy now and I feel fine. I can climb a tree ...

Teddy Ryder, July 10, 1922.

Photograph of Teddy Ryder and his sister, Margaret, April 1923.

Teddy Ryder. Letter to F.G. Banting. Nov. 6, 1923.

I wish I could see you. I am feeling fine now. I would like to go to Toronto to see you ... I sent you my picture with Margaret. Do you know me now?

Newspaper clipping: "Teddy Ryder: Banting's living miracle." Sunday Star, Feb. 20, 1983.

The article was written by *Star* reporter, Frank Jones who interviewed both Ted Ryder and his mother (then in her nineties) at their home in Hartford, Conn. Both Ted and his mother had vivid memories of the months they spent in Toronto in 1922. University of Toronto historian, Professor Michael Bliss, author of *The Discovery of Insulin*, had discovered that Ryder was still alive when he met Ryder's doctor after giving a lecture to a medical history group at Yale University. Ted Ryder died in 1993, at the age of seventy-six, having lived for over seventy years on insulin.



Teddy Ryder, July 10, 1923.

Chart for Ruth Whitehill. June 1922.

Eight year old Ruth Whitehill became a private patient of Banting's in mid June. She had been brought for treatment to Toronto from her home in Baltimore where she was a patient of Dr. Louis Hamburger. She received her first injection of insulin on June 17, made satisfactory progress throughout the summer and was able to return home at the end of September.

Ruth Whitehill. Letter to F.G. Banting, Nov. 10, 1922.

Dear Dr. Fred. I wish you would come to see us soon. I miss you very much. I am going to a childrens play this afternoon. Must stop to dress. Love, Ruth Whitehill.

Myra Blaustein. Letter to F.G. Banting, Dec. 21/22.

The same day you left I gathered some nerve together and gave myself the Insulin and doing it ever since [sic]. I have been sugar free for the last five days and getting about 1900 calories consisting of Pro. 60 Fat 163 Ch. 44. I am feeling great and getting Insulin only twice a day ... A Merry Christmas and a Happy New Year to all of you. I remain, your little friend Myra. P.S. I gained 2 1/2 pounds last week.

Myra, like Ruth Whitehill, had come to Toronto from Baltimore to become one of Banting's private patients. She had returned home at the same time as Ruth Whitehill and continued to improve under the care of Dr. Hamburger.

Janet Turnbull. Letter to F.G. Banting, with a photograph. Undated. ca. Nov. 1923.

I am feeling so good and getting so much to eat. I get oatmeal and potato. I was in the Halloween parade and got a prize. Here are some pictures. Dont I look fat?

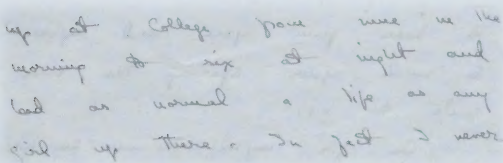
Six year old Janet Turnbull was admitted to Toronto General Hospital on August 20, 1922. Her condition must have improved rapidly as she was discharged Sept. 22 and returned to her home near Pittsburg, Penn. Her mother kept detailed charts of her progress which show how difficult it was for a young diabetic child to stay on a strict diet. After Janet had been discovered taking a spoonful of jelly as she cleared the dishes from the table and then eating peanuts she had been given by a neighbour, her mother wrote in despair to Banting:

She is like a periodic drinker. Will resist temptation for food for weeks, then when she begins to break out seems unable to stop.

Many diabetics experienced similar struggles.

Case 7

CONTINUING SUCCESS



*up at College gave me the
morning to six I night and
had as normal a life as any
girl up there. In fact I never*

“As normal a life as any girl”

*Elizabeth Hughes, Letter to
F.G. Banting, Nov. 2, 1926.*

Toronto General Hospital. Patient records for Mrs. Charlotte E. Clarke, showing her admission on July 9 and discharge on Sept. 2, 1922.

Dr. L.C. Palmer. Notes on Mrs. Charlotte Clarke, July-August 1922.

These notes record the first operation on a diabetic utilizing the new insulin treatment.

Charlotte Clarke, a diabetic woman in her fifties, had developed gangrene in her leg from an unhealed cut in her foot. Dr. Palmer, dubious about her chances of surviving the surgery, consulted Dr. Banting who advised amputation and prescribed treatment with insulin. After the operation in Dr. Palmer's opinion "it did not seem possible that she could get better". After receiving insulin for several days, however, her wound began to heal, but when the supply of insulin ran out, the wound reopened.

The outlook was most discouraging for it did not seem possible to ever get the wound to heal again. Dr. Banting, on returning to the city, started the patient on a fresh supply of Insulin, the wound immediately started to heal

and became a firm hard scar. On August the 5th the patient was free of sugar for the first time in six years ... I may state that Mrs. Clarke is now in good health, she looks at least 40 years younger and gets around freely, does her own housework and cooked [sic] the meals for her family.

Antoinette C. Hughes, Washington, D.C. Letter to F.G. Banting, July 3, 1922.

Mrs. Hughes, wife of Charles Hughes, then American Secretary-of-State, wrote to Banting to ask him to treat her fourteen year old daughter, Elizabeth, who had suffered from severe diabetes for the past three years.

She is pitifully depleted and reduced. She is five feet tall and weighs less than fifty pounds ... She is a model patient having never once in these three years, gone over her diet ... we feel that this strength of character — which her nurse considers quite unusual — is, of course, much in her favor.

Banting refused Mrs. Hughes initially, citing the shortage of insulin, but by August agreed to treat Elizabeth in Toronto. She would become one of his greatest success stories.

Dr. Frederick M. Allen, The Physiatric Institute, Morristown, N.J. Letter to F.G. Banting, Aug. 12, 1922.

You will find Elizabeth a model patient in all respects ... There could not be a child, who for her own self deserved your care more than Elizabeth ...

Elizabeth Hughes had been one of Dr. Allen's first patients at his Institute in 1919. He had continued to monitor her condition over the next three years while she lived at home with a specially trained nurse.

F.G. Banting. Notes on examination of Elizabeth Hughes, Aug. 16, 1922.

Wt. 45 lbs. height 5 ft. patient extremely emaciated ... She was scarcely able to walk on account of weakness ...

Charts for Elizabeth Hughes, Aug.-Dec. 1922.

The entries record Elizabeth's treatment, medical condition and diet from August 16/17, when she received her first injection of insulin, to her departure from Toronto on Nov. 30. During that time her weight increased from 45 to 79 pounds and her average calory intake went from 1125 to 2512.

The entries are in Elizabeth Hughes's own hand. She had been keeping charts like these since she was first diagnosed in 1919, and continued her meticulous record-keeping over the next two years, regularly forwarding the charts to Banting with her letters describing her progress.

Newspaper clipping: "Daughter of Secretary of State Tries New Toronto Discovery." Toronto Daily Star, Aug. 17, 1922.

Newspaper clipping: "Miss Hughes, Ill, Takes New 'Cure'." Toronto, Oct. 17 [1922]

Elizabeth Hughes, Washington, D.C. Letter to F.G. Banting, Jan. 1, 1923.

I weigh 84 3/4 pounds now ... I ride horseback for an hour three times a week and am thinking of swimming in our fine Y.W.C.A. pool the other three days. I am beginning to take two courses at school on Jan. 9th and I am eagerly looking forward to it.

Photograph of Elizabeth Hughes. 1923.

Elizabeth Hughes, Washington, D.C. Letter to F.G. Banting, Feb. 10, 1924.

This winter I am going to school and am taking three rather difficult courses which require a great deal of studying, so that taking all in all, my life at the present time is just like that of a normal person.

Elizabeth Hughes, New York City, N.Y. Letter to F.G. Banting, Nov. 2, 1926.



*Newspaper clipping from
Toronto Daily Star,
Aug. 17, 1922.*

As for myself I am so well that I am afraid I have nothing much to report ... This year I am continuing my course at Barnard College and I am working full time in the hopes of receiving a degree in a couple of years. I am up at College from nine in the morning to six at night and lead as normal a life as any girl up there.

Newspaper clipping from F.G. Banting's Scrapbook: "Daughter of the Chief Justice on her Honeymoon: Mr. and Mrs. W.T. Gossett Who Were Married Recently in Washington, Out for a Bicycle Ride in Bermuda." [1930]

Elizabeth Hughes graduated from Barnard College in 1929 and in 1930 married William T. Gossett, a young lawyer in her father's law firm. Gossett went on to a distinguished career in law and became president of the American Bar Association. He and Elizabeth had three children.

In later years Elizabeth became a Trustee of Barnard College, and a founding Trustee of Oakland University in Rochester. In 1972 she founded the Supreme Court Historical Society and served as its President for many years. None of her friends or associates ever knew that she suffered from diabetes.

Photograph of Elizabeth Hughes with her husband and three children. 1980. (Lent by Professor Michael Bliss)

Lowell Eklund. "A Tribute to Elizabeth Hughes Gossett. Memorial Service, April 28, 1981." Christ Church, Cranbrook, Bloomfield Hills, Mich. (Lent by Professor Michael Bliss)

Elizabeth Hughes died from a heart attack in 1981. She was seventy-three and had lived for fifty-eight years on insulin.

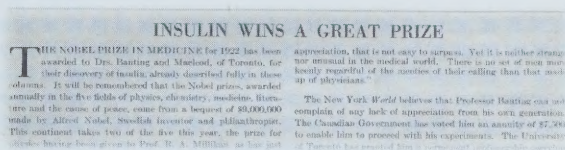
Medal Insulin Cymru. The Elizabeth Evans Hughes Welsh Insulin Medal. 1995.

In 1995 the Eli Lilly Company commissioned a number of Welsh Insulin Medals to honour Welsh diabetics who had lived with the aid of insulin for fifty years or more. The medal honours Elizabeth Evans Hughes as “one of the first children to be treated with insulin in 1922” and commemorates her Welsh background. Elizabeth’s Welsh middle name, “Evans”, was a family name which she herself used in her signature and on her stationary.

The image of Elizabeth Hughes on the medal was based on the 1923 photograph displayed in this case.

Case 8

GROWING RECOGNITION



“Insulin Wins a Great Prize”

Literary Digest, *New York*, Dec. 8, 1923.

Photograph of Elsie Needham, “The first child to recover from coma by the use of insulin.”

In October 1922 eleven year old Elsie Needham was admitted to the Hospital for Sick Children in a diabetic coma, after gorging herself on grapes and olives. She was treated with insulin by Dr. Banting and Dr. Gladys Boyd, head of the Hospital’s new diabetic clinic. Elsie was revived from her coma, regained her strength, and had recovered sufficiently to be back at school in January. Prior to the discovery of insulin, diabetics who lapsed into coma invariably died.

Photographs of patients before and after insulin treatment. 1923.

These photographs illustrated the article entitled “The Use of Insulin in Juvenile Diabetes”, by H. Rawle Geyelin *et al.*, published in the *Journal of Metabolic Research*, edited by F.M. Allen, vol. 2, nos. 5-6 (1922-23).

Elsie Needham, mid 1920s.



F.G. Banting, C.H. Best, J.B. Collip, J.J.R. Macleod and E.C. Noble. *"The Effects of insulin on Experimental Hyperglycemia in Rabbits."* Reprinted from the *American Journal of Physiology*, vol. 62, no. 3 (Nov. 1922).

In December 1921 Collip had developed a method for testing the strength of batches of insulin by testing the blood sugar of normal (not diabetic) rabbits. He then observed that rabbits whose blood sugar fell below certain levels went into convulsions and died. Death could be averted, however, if injections of glucose were given. Similar observations of hypoglycemic reactions were made at the same time by Macleod and by Clark Noble, who had recently joined the research team.

F.G. Banting, W.R. Campbell, and A.A. Fletcher. *"Insulin in the Treatment of Diabetes Mellitus."* Reprinted from the *Journal of Metabolic Research*, edited by F.M. Allen, vol. 2, nos. 5-6 (1922-23).

Among the cases discussed in this paper was that of Elizabeth Hughes. Others include several patients treated in the new diabetic clinic at Toronto General Hospital where both Campbell and Fletcher were on staff.

G.H.A. Clowes, Lilly Research Laboratories, Indianapolis. Letter to J.J.R. Macleod, Feb. 23, 1923. (Lent by Connaught Laboratories Archives)

We are now in a position to produce at comparatively short notice enough insulin to take care of the entire needs of the United States and Canada, at least so long as any sort of restrictions are imposed.

Both the Connaught and Lilly Laboratories had experienced difficulties and shortfalls in their insulin production during the initial months of manufacture, but by early 1923 Clowes was confident most of the problems had been overcome and insulin could be made more widely available.



First insulin plant, old Y.M.C.A. Building, 1923.

Photographs of the Connaught Laboratories' insulin production unit, 1923. (Copied from originals in the Connaught Laboratories Archives)

Insulin was first manufactured in the basement laboratories of the Medical Building under somewhat makeshift conditions. In 1923 Connaught Laboratories moved its insulin production unit into the old Y.M.C.A. building on College St. which had been vacant since the Y. had moved into the newly opened Hart House. Insulin was produced here until 1927.

Insulin Committee, University of Toronto. *"Insulin: Its Actions, Its Therapeutic Value in Diabetes, and Its Manufacture."* Reprinted from the *Journal of the American Medical Association*, vol. 80, (June 1923).

Ontario. Provincial Board of Health. Insulin. Information for Physicians regarding Free Distribution of Insulin in Suitable Cases of Diabetes. Toronto, 1923.

Eli Lilly & Company, Indianapolis. One 5 c.c. vial of Iletin. With a cardboard box. Dated Oct. 16, 1922.

Connaught Laboratories, University of Toronto. One 5 c.c. vial of insulin. Dated Nov. 5, 1923.

Connaught Laboratories, University of Toronto. Four 10 c.c. vials of insulin. With cardboard box. Labelled with expiry date of Jan. 21, 1925. Accompanied by "Insulin Direction Sheet".

These vials are lent by the Connaught Laboratories Archives from Dr. Albert Fisher's collection of insulin artifacts, recently donated to the Archives.

Hjalmar Forssner, Principal of the Royal Karolinska Institute, Stockholm. Telegram to F.G. Banting, Oct. 25, 1923.

The Royal Caroline Institute has presented to you together with Professor W.[sic] J.R. Macleod the Nobel Prize of the year 1923.

This was the first time a Canadian had been awarded a Nobel Prize.

F.G. Banting. Draft of telegram to C.H. Best, c/o Elliott P. Joslin, Boston, Mass., Oct. 26, 1923.

Nobel trustees have conferred prize on Macleod and me — you are with me in my share always — Fred.

F.G. Banting. Telegram to E.P. Joslin, Boston, Oct. 26, 1923.

At any meeting or dinner please read the following stop I ascribe to Best equal share in discovery stop hurt that he is not so acknowledge [sic] by Nobel trustees stop will share with him. Banting.

When Banting received the telegram announcing that he and Macleod had been jointly awarded the Nobel Prize in Medicine, his first reaction was anger that he would share the honour with Macleod and not with Best. He considered refusing the Prize but instead decided to share his half with Best. The next day he drafted a telegram to Best, who had gone to Boston to give a lecture at the Harvard Medical School.

Banting then sent a wire to Dr. Joslin, with whom Best was staying, asking that Joslin make a public announcement. That evening, after Best had given his lecture, Joslin read Banting's telegram to the surprised audience who broke out into loud applause.

Newspaper clipping: "Macleod Awards Collip Half of his Nobel Prize. Total of \$40,000 Has Now Been Divided Equally Among Four." Toronto Daily Star, Nov. 7, 1923.

A quote from Macleod reads:

Doctors Banting and Best showed by their experiments that insulin was present in extracts of the pancreas. It was then that Dr. Collip came in and with his

assistance it was shown that it was possible to produce insulin suitable to continued use.

When the interviewer asked Macleod about his role in the discovery, Macleod is quoted as replying modestly, "Oh, I was only the impresario — the managing director."

"Science and Invention. Insulin Wins a Great Prize", Literary Digest, Dec. 8, 1923.

This short article, unlike most of the Nobel Prize press coverage, features photographs of each of the four scientists and comments that the decision to share the Prize equally is a "fine example of professional generosity and practical appreciation that is not easy to surpass."

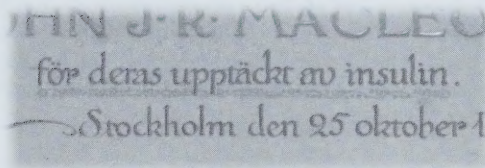
Newspaper clippings on a page from F.G. Banting's Scrapbook:

"University honors men whose achievements have honored it. Talented workers in research field paid high honors." Globe, Nov. 27, 1923.

"University honours Professors Banting and Macleod as winners of the Nobel prize Award for Medicine in Board of Governors' banquet held at Hart House." Globe, Nov. 27, 1923.

Maclean Hunter Room: Case 9

THE NOBEL PRIZE



"för deras upptäckt av insulin"

Nobel Prize Citation, 1923.

Nobel Medal inscribed to F.G. Banting. 1923.

Nobel Prize Citation inscribed to F.G. Banting. 1923.

A hand-illuminated address in a magnificent gold-tooled binding.

F.G. Banting. Diabetes and Insulin; Nobel Lecture delivered at Stockholm on September 15th 1925. Stockholm, 1925.

Banting's Nobel lecture outlined in some detail the several stages in the discovery and development of insulin. In this account Banting gave Collip the credit for the initial purification of the extract and cited Best as the person chiefly responsible for solving the large scale production problems. The remainder of his speech described some of the clinical results of insulin treatment and mentioned the cases of Elizabeth Hughes and Elsie Needham.

This copy of the lecture was inscribed by Banting to his mother and father.

Case 10

CONTROVERSY

...
...d to seize this opportunity to put in writing my
...k regard to the most unfortunate misunderstandings
...sion concerning questions of priority and the credit
...e given to those responsible for the discovery of
...f by so doing I can help to retain for the University
...e reputation which it has already acquired, through

“the most unfortunate misunderstandings”

*J.J.R. Macleod, Letter to
Colonel Albert Gooderham, Sept. 20, 1922.*

Colonel Albert Gooderham. Letter to F.G. Banting, Sept. 16, 1922.

Gooderham, as Chairman of the Board of Governors at the University, was anxious to effect a reconciliation between Banting, Best and Macleod. He feared the negative publicity would damage the reputation of the University and believed the lack of agreement would compromise the work of the Insulin Committee and complicate the securing of patents.

Gooderham wrote to each of the three men requesting their accounts of the discovery “right from the start”. Since Collip was no longer at the University he asked each to outline Collip’s role as well. He planned to “compare these statements and see wherein they differ, and ask you three gentlemen to meet at any early date with a view to harmonizing these statements with me”.

Each man wrote his account and sent it to Gooderham but no harmonizing proved possible. Gooderham kept the statements to himself. The original documents have never been found, but copies were eventually discovered in the papers of Banting, Best, Macleod, and Collip and were published in 1978 and 1982.

F.G. Banting. [Account of the discovery of insulin, Sept. 1922] Carbon copy of typescript.

Banting’s thirteen page account details many of his grievances against Macleod and contains an attack on Collip whom Banting here blamed for the insulin “famine” in the spring of 1922. This account was first published by Professor Michael Bliss in the *Bulletin of the History of Medicine*, vol. 56 (1982).

J.B. Collip. Letter to F.G. Banting, July 7 [1925]

This letter was written in answer to a note which Banting had written to Collip congratulating him on a recent paper and expressing the hope that they could bury the past. Collip replied:

Personally I regret very much the unfortunate misunderstandings of the hectic winter of ‘22 and I would be only too glad to put them in the background of oblivion. With a hearty hand shake in spirit and the best of luck to you.

Banting and Collip did become good friends in later life.

J.J.R. Macleod. “History of the Researches Leading to the Discovery of Insulin.” Sept. 20, 1922. Carbon copy of typescript.

J.J.R. Macleod. Letter to Colonel Albert Gooderham, Sept. 20, 1922. Carbon copy of typed letter.

I am glad to seize this opportunity to put in writing my position with regard to the most unfortunate misunderstandings which have arisen concerning questions of priority and the credit that should be given to those responsible for the discovery of Insulin.

Macleod goes on to state that he is “entirely bewildered” by charges he had not given sufficient credit to Banting and Best, pointing out that he had declined their invitation to add his name to the first published report of their work.

In the final paragraph of his account Macleod sums up his view of the past year’s achievements and of his own role in these.

Through concentrated effort, for the co-ordination of which I have been responsible, we have given to Science in little more than one year a practically completed piece of research work - we have proved the value of Insulin ...

A copy of this letter and the accompanying twenty page statement were discovered after J.J.R. Macleod’s death in his private papers. The copy on display, however, comes from the papers of J.B. Collip to whom Macleod sent it in Sept. 1922. The letter and the statement were published by Lloyd Stevenson in the *Bulletin of the History of Medicine*, vol. 52 (1978).

J.B. Collip. [Drafts of a statement on his contribution to the development of insulin in 1921 and 1922. 1922]

After Collip received Macleod’s letter and a copy of his statement, he drafted a reply containing his own account of events in 1921-22. The draft exists in a fragmentary form as part of an unsent letter to Macleod and as a carbon copy of a typescript. The typescript and drafts were found in Collip’s papers after his death. The typescript was subsequently published by Professor Michael Bliss in the *Bulletin of the History of Medicine*, vol. 56 (1982).

C.H. Best. “A Report of the Discovery and the Development of the Knowledge of the Properties of Insulin” [Sept. 1922] Carbon copy of typescript. (Lent by Dr. Henry Best)

Best’s four page statement was concise and modest in tone. He does voice his regret, however, that he was not able to carry out experiments which he and Banting had discussed but which were later carried out by Collip. He concludes his statement on an unintentionally ironic note.

My report of the development of this work is given in less detail than I had previously intended doing, caused through conversation with Dr. Banting and Dr. MacLeod [sic]. I am sure there will be very few controversial points.

This account was published by Professor Michael Bliss in the *Bulletin of the History of Medicine*, vol. 56 (1982).

Case 11

BEFORE THE DISCOVERY

YOUNG FRED BANTING

Photograph of the children of William and Margaret Banting. Alliston, Ont., ca. 1892-1893.

Fred Banting, born in 1891, is the youngest child in this family group. He wears a lace collar, and sits beside his brother, Kenneth. Nelson is standing with Esther next to him and Thompson is seated on the floor.

Photograph of Fred Banting and Wes Dungey, ca. 1910 (Reproduced from original in the possession of Edward Banting)

Photograph of Fred and his friend, Wes Dungey, ca. 1910-11. The caption in the original album reads: "when they played on the Alliston ball team in 1910 or 1911".

Photograph of Fred in uniform with friends at Alliston, 1915.

Fred's girl friend, Edith Roach, is beside him. Fred had enlisted in the army in 1915 and spent much of the summer at training camp at Niagara. He finished his medical degree in December 1916, and was sent overseas in March 1917.



Fred Banting, Edith Roach, and friends, 1915.

Shot-Put Medal awarded to Staff Sergeant F.G. Banting. Niagara Camp, 1915.

F.G. Banting. Letter to his mother, Margaret Banting, Alliston, Sept. 29, 1918.

This letter will be short left hand. I was slightly wounded yesterday in the right forearm. Had operation last night and shrapnel [drawing] size removed from between bones. No fracture but ulna bone damaged. I feel petty [sic] good, only tired ... Now please dont worry. I am the luckist [sic] boy in France ... With love from Fred.

Banting had been sent to France with the 13th Field Ambulance in June 1918 after several months of work as an orthopaedic surgeon at Granville Canadian Special Hospital in Buxton,

England. Subsequently he was posted as medical officer to the 44th Battalion, 4th Canadian Division. He was wounded during the assault on Cambrai on Sept. 28.

F.G. Banting. Letter to his mother, Margaret Banting, Alliston, Oct. 15, 1918.

Im up again today but I had a little haemorrhage [sic] again Sunday. My mail all arrived from the Ambulance this morning ... And Mother a letter from the second in command and don't tell any person but I have been recommended for the military cross. Just at present I'd sooner have it than the F.R.C.S.

Banting spent more than two months recuperating from his wound, and was not released from hospital until December 1918.

Military Cross awarded to F.G. Banting, 1919.

The official citation, published in the *Canada Gazette*, 1919, reads:

Capt. Frederick Grant Banting, 13th Fld. Amb., C.A.M.C. Near Haynecourt on September 28th, 1918, when the medical officer of the 46th Canadian Battalion was wounded, he immediately proceeded forward through intense shell fire to reach the battalion. Several of his men were wounded and he, neglecting his own safety, stopped to attend to them. While doing this he was wounded himself and was sent out notwithstanding his pleas to be left at the front. His energy and pluck were of a very high order.

CHARLEY BEST



Photograph of young Charley Best with his sister Hilda and his mother, Lulu Fisher Best, ca. 1905. (Lent by Dr. Henry Best and reproduced from original in his possession)

The Best family lived in West Pembroke, Maine where Charley's father was a doctor. Herbert Huestis Best, had grown up in Nova Scotia but had completed his medical training in New York City and had settled in Maine shortly after graduating.

Photograph of Charley Best as an undergraduate at the University of Toronto, ca. 1918.

Photograph of Charley Best in military uniform, ca. 1918.

Photograph of Charley Best on horseback at Petawawa, Ont., 1918.

After several fruitless attempts to enlist in 1917, Charley finally found a doctor who overlooked his heart murmur and certified him as fit for service. In 1918 he was accepted for service in the 70th Battery

Charles Best as an undergraduate, ca. 1918.

of Horse Artillery. After training at Petawawa, he was sent overseas, with the rank of sergeant. Charley spent the fall at a training camp in Wales, but the war was over before he could achieve his desire of seeing action in France. By the winter of 1919 he was back at the University, picking up his second year in Honours Science.

Photograph of Charley Best and Clark Noble, Georgetown, Ont., 1920.

Both Charley and his friend and classmate, Clark Noble, played on the Georgetown baseball team in the summer of 1920. Georgetown was Clark's home town.

Photograph of Charley Best with his friends Henry Marsh and Clark Noble. (Lent by Dr. Henry Best and reproduced from the original in his possession)

The triple portrait was taken during Charley Best's undergraduate years at University College, probably in his graduating year. He and Clark Noble were both taking Honours Physiology and Biochemistry.

BERT COLLIP

Photograph of the Collip family, Belleville, ca. 1898.

Young Bert with his father, James Denis Collip and his mother, Mahala Frances Vance Collip.

Graduation photograph of Bert Collip, 1912.

Bert graduated from Trinity College, University of Toronto, with a B.A. in Honours Physiology and Biochemistry in 1912.

Photograph of Bert Collip as a graduate student, ca. 1914-15.

Bert received his M.A. in 1913 and his Ph.D. in biochemistry in 1916, working under the direction of Professor A.B. Macallum at the University of Toronto.

Photograph of Bert Collip with his fiancée, Ray Vivian Ralph, ca. 1915.

Ray and Bert were married in 1915.

J.B. Collip. "Internal Secretions." Reprinted from the Canadian Medical Association Journal, Dec. 1916.

Offprint of Collip's first paper. When he wrote this paper Collip was a lecturer in the Department of Physiology at the University of Alberta in Edmonton.



J.B. Collip as a graduate student, ca 1914-15.

J.J.R. MACLEOD



J.J.R. Macleod, 1906.

Photograph of J.J.R. Macleod, 1906. (Reproduced from photograph held by the University Archives, Case Western Reserve University, Cleveland, Ohio)

Macleod had graduated from the University of Aberdeen's School of Medicine in 1898. After two years of graduate study at Aberdeen and at Leipzig, he was appointed lecturer in biochemistry at the London Hospital Medical College. In 1903 he accepted an appointment as Chairman of Physiology at Western Reserve University in Cleveland, Ohio.

J.J.R. Macleod. "Various Forms of Experimental Diabetes and their Significance for Diabetes Mellitus." Reprinted from the Journal of the American Medical Association, vol. 55 (Dec. 17, 1910).

By 1910 Macleod had already carried out considerable research into carbohydrate metabolism.

J.J.R. Macleod. Diabetes: Its Pathological Physiology. London: Edward Arnold, 1913.

This work is based on a series of eight lectures which Macleod delivered in the summer of 1912 at the London Hospital. This book helped establish Macleod as a leading authority in the field of carbohydrate metabolism.

J.J.R. Macleod. Letter to Sir Robert Falconer, President, University of Toronto, [Dec. 1917] (Lent by the University of Toronto Archives. Falconer Papers. A67-0007/48B)

Macleod writes to accept the position of Professor of Physiology at the University of Toronto. He and his wife moved to Toronto in June 1918.

J.J.R. Macleod. Physiology and Biochemistry in Modern Medicine. St. Louis: C.V. Mosby, 1918.

This work, intended primarily as a textbook for medical students, proved immensely popular, going through seven editions in the next seventeen years.

AND AFTERWARDS

SIR F.G. BANTING

Canadian National Exhibition medal. 1923.

Designed by Emanuel Hahn, this beautiful medal in a special silver case was presented to Banting on the occasion of his opening the C.N.E. on August 25, 1923. The invitation to open the Exhibition in Toronto was one of the earliest civic gestures of recognition for Banting.

Ontario. Legislature. Bill no. 200. An Act to provide for an Annual Grant to the University of Toronto for the promotion of Medical Research. 1923.

This bill, which passed into law in May, provided \$10,000 for the establishment of the Banting and Best Chair of Medical Research at the University of Toronto. Banting was appointed to the Chair as Professor of Medical Research. Later the title was changed to the Banting and Best Department of Medical Research.

The Banting Research Foundation, Toronto, Canada. A Short Resumé of its Creation, Purposes and Organization. [1925]

Sir William Mulock and Sir Robert Falconer launched a major fundraising campaign for a private endowment to increase support for the Banting and Best Chair of Medical Research and to fund future medical research projects at the University of Toronto and elsewhere. Public enthusiasm ensured that the campaign's goal of \$500,000 was quickly reached.

Programme for formal opening of the Banting Institute and special convocation for the conferring of honorary degrees in Convocation Hall, Tuesday, September 16th, 1930.

Photograph of the Banting Institute, 1930.

This new building provided much needed medical laboratory and office space for several University departments. The Banting and Best Department of Medical Research was given the top floor of the building.

Photograph of F.G. Banting at his desk in the new Banting Institute, ca. 1930.

Two small canvases painted by Banting hang on the office wall behind his desk.

Insignia presented to F.G. Banting when he was invested as Knight Commander of the Civil Division of the Order of British Empire in 1934.

In 1919 the Canadian government had suspended the practice of Canadian citizens receiving British titles, but when the custom was revived in 1934, Banting immediately received a knighthood.

F.N.G. Starr medal awarded to F.G. Banting by the Canadian Medical Association. 1936.

Photograph of J.B. Collip, C.H. Best, Mrs. F.N.G. Starr, and F.G. Banting. Victoria, B.C., June 1936.

In June 1936 at its annual meeting in Victoria, B.C., the Canadian Medical Association honoured the three surviving co-discoverers of insulin, J.B. Collip, F.G. Banting, and C.H. Best, with the F.N.G. Starr award. Established by the C.M.A. in memory of its former president, Dr. Frederick Newton Gisborne Starr, the award was described as “the highest honour for the profession of Medicine in Canada”. This photograph is the only one which shows the three co-discoverers of insulin together.

F.G. Banting. [The story of the discovery of insulin] London, England, 1940. Holograph manuscript.

After the outbreak of the Second World War, Banting was sent to England by the National Research Council of Canada to survey the state of British military research and determine the role that Canadian research could play. While he was in London, Banting occupied some of his evenings by writing what he obviously intended to be his definitive account of the discovery of insulin.

On many occasions and by many people I have been asked to write the story of the discovery of Insulin. I have always thought that Science was greater than the individual and that Insulin therefore spoke for itself and the story needed no further telling ... There were bitter feelings that could only be relieved by time ... Now twenty years have taken away all bitterness.

Banting's introductory remarks conclude with a statement of what he believed to be his most valuable overall achievement — his building of a team of dedicated research scientists and providing them with the excellent laboratory facilities of the Banting Institute.

My work only commenced when insulin was an accomplished fact ... I have helped to build a group of young men who form an institution that will live when all who now live are long since dead. Today my greatest joy is in the accomplishments of this group.

The lengthy manuscript, contained in several notebooks, was never finished or revised and remains unpublished.

Photograph of Major F.G. Banting, Feb. 14, 1941.

The last photograph of Banting, taken shortly before he travelled to Gander, Nfld. in preparation for a flight to England.

Newspaper clippings: “Banting Plane Found”, Toronto Daily Star, Feb. 24, 1941. “Illustrious Soldier-Scientist, Major Sir Frederick Banting Goes to His Last Rest”, Globe and Mail, Mar. 5, 1941.

Photograph of the crashed airplane in which Banting lost his life. Feb. 1941.

Banting was en route to England when his plane, a Lockheed Hudson bomber, crashed on the east coast of Newfoundland on Feb. 20, 1941. Shortly after take-off from Gander the plane

had developed mechanical problems. The pilot, J.C. Mackey, attempted to bring the plane down near Musgrave Harbour but hit a tree on landing. Both the radio operator and the navigator were killed by the impact and Banting was fatally injured. He died the following day. The pilot survived and was rescued several days later.

The funeral service for Banting was held on March 4 in Convocation Hall at the University of Toronto.

J.B. Collip. *“Frederick Grant Banting, Discoverer of Insulin.” Reprinted from the Scientific Monthly, vol. 52 (May 1941).*

In this obituary Collip pays tribute to Banting’s determination and perseverance and refers to his own role in the discovery in extremely modest terms.

I feel that I was very fortunate to have been a worker in Macleod’s laboratory at the time that Banting started his first investigations and to have known of the progress of this work at first hand ... The part which I was able to contribute subsequently to the work of the team was only that which any well-trained biochemist could be expected to contribute, and was indeed very trivial by comparison with Banting’s contribution.



Major F.G. Banting, February 14, 1941.

C.H. Best. *“Frederick Grant Banting: 1891-1941.” Reprinted from Obituary Notices of Fellows of The Royal Society, vol. 4 (Nov. 1942).*

Best’s tribute to Banting concludes:

The Banting Institute, the Banting Foundation, and the Banting Memorial Lectureship, have been created in the University of Toronto as tangible tributes to him, but his name will live for ever in the hearts of successive generations of diabetics and in the minds of young investigators who will be stimulated by his brilliant and fearless career.

DR. CHARLES H. BEST

Photograph of C.H. Best in the Sir William Bayliss Laboratory at the University of London, England, 1928.

After getting his M.B. from the University of Toronto in 1925, Best went to England to do post graduate work with Sir Henry Dale at the National Institute for Medical Research. Here he was part of the research team which discovered histamine. Best received his D.Sc. from the University of London in 1928.

J.J.R. Macleod, Aberdeen. Letter to C.H. Best, Toronto, Jan. 26, 1929.

Heartiest congratulations on being appointed my successor. I wish you all success and prosperity in your new job.

Best had just been appointed to the Chair of the Physiology Department which had been formerly held by Macleod. In 1928 Macleod had resigned the Chair and returned to Scotland to become Regius Professor of Physiology at the University of Aberdeen.

Photograph of Surgeon Captain Charles H. Best, Royal Canadian Navy. ca. 1940.

During the Second World War, Best held the rank of Surgeon Captain in the Royal Canadian Navy. In 1939 he initiated a method of drying and storing blood serum so it could be shipped directly to field hospitals on the battlefields for use as needed. This project was then developed further by the Connaught Laboratories in collaboration with the Canadian Red Cross Society.

In 1941 Best organized the Medical Research Division of the Royal Canadian Navy and became its Director. Throughout the war he and his associates worked on a number of projects for the Navy, including the enhancement of night vision, remedies for seasickness, and designs for protective clothing to safeguard against exposure.

Newspaper clipping: "Collaborator of Banting, Dr. C.H. Best succeeds him." Toronto Daily Star, Toronto, April 26, 1941.

After Banting's death in 1941, Best was appointed director of the Banting and Best Department of Medical Research, a position he retained until his retirement in 1967. During these years Best continued to publish papers, usually as part of a research team, on insulin and diabetes, choline and liver damage, heparin and thrombosis.

Photograph of C.H. Best in his laboratory, University of Toronto, spring 1948.



Photograph of the Charles H. Best Institute, University of Toronto. 1953.

The building stands on College St. just west of the Banting Institute and is built in a similar architectural style. A bridge connects the upper floors of the two Institutes and was intended to symbolize the close connection between the two men for whom the buildings are named.

The Charles H. Best Institute, University of Toronto. Opening Ceremonies. Reprinted from Diabetes; the Journal of the American Diabetes Association, vol. 3, no. 1 (Jan.-Feb. 1954)

The C.H. Best Institute was officially opened on Sept. 15, 1953. The speeches and lectures delivered on that occasion were collected and reprinted in this booklet.

C.H. Best in his laboratory, 1948.

Reproduction of a portrait of C.H. Best by Cleeve Horne., R.C.A., O.S.A., 1953.

The original oil painting was presented at the official opening of the Charles H. Best Institute and now hangs in the entrance foyer of the Institute.

C.H. Best. Selected papers of Charles H. Best. Toronto: University of Toronto Press, 1963.

This volume contains over sixty papers and speeches given by Best, dating from his first publications with Banting in 1922, to papers and speeches given forty years later, together with brief autobiographical notes.

Program for a Dinner and Presentation in honour of Charles Herbert Best, Thursday, June 15th, 1967.

Best formally retired in 1967 but continued to serve as consultant to both the Connaught Laboratories and the Banting and Best Department of Medical Research until his death in 1978.

Companion of the Order of Canada insignia. Awarded in 1967. (Lent by Dr. Henry Best)

One of the many honours which Best received during his lengthy career.

Photograph of C.H. Best and Margaret Best, Dec. 16, 1971.

This photograph was taken in London, England on the day Best was invested as a Companion of the Order of the British Empire by Her Majesty Queen Elizabeth II.

"Memorial service for Charles Herbert Best ... 12:00 Noon, Monday, 3 April, 1978, Convocation Hall, University of Toronto."

C.H. Best died on March 31, 1978 at the age of 79.

Dr. A.L. Chute gave the eulogy at the memorial service. He described Best as "an outstanding scientist, teacher, humanitarian, and world citizen".

DR. J.B. COLLIP

Photograph of J.B. Collip in his laboratory at the University of Alberta, ca. 1927.

Collip returned to the University of Alberta in June 1922 to take up his appointment as Head of the Department of Biochemistry. He continued his research on insulin but his major achievement during his Alberta years was his pioneering work in the discovery of the parathyroid hormone which he was able to isolate in 1925.

Photograph of J.B. Collip in his office in the Department of Biochemistry at McGill University, ca. 1930.

In 1928 Collip accepted the Chair of Biochemistry at McGill. In his McGill laboratory, with a large research team, he worked on describing placental and pituitary hormones. In 1933 he was responsible for isolating the adrenocorticotrophic hormone of the anterior pituitary, known as ACTH.

Photograph of J.B. Collip as Acting Lieutenant-Colonel, Royal Canadian Army Medical Corps, ca. 1942.

From 1942 on Collip served as Medical Liaison Officer to the Office of the Surgeon General in Washington, D.C. In 1944 he was given the rank of Acting Colonel in the Royal Canadian Army Medical Corps.

Throughout the war Collip was an active member of the National Research Council's Associate Committee on Medical Research, becoming Chairman after Banting's death in 1941. In addition he was Chairman of the N.R.C.'s Co-ordinating Committee and was thus responsible for overseeing all the naval, army, and aviation medical research being carried out across the country.



J.B. Collip and Sir Henry Dale, 1947.

Companion of the Order of the British Empire insignia.

Collip was awarded this honour in 1943 in recognition of his contributions to wartime research.

Photograph of J.B. Collip and Sir Henry Dale at the entrance to the Collip Medical Research Laboratory, University of Western Ontario, 1947.

In 1947 Collip accepted the position of Dean of Medicine and Professor of Medical Research at the University of Western Ontario. The new Department of Medical Research was housed in a building named in Collip's honour, the Collip Medical Research Laboratory.

Photograph of J.B. Collip and his wife at the dedication of a plaque commemorating the isolation of the parathyroid hormone in the Department of Biochemistry at the University of Alberta in 1925. University of Alberta, Edmonton, June 12, 1959.

Banting Medal of the American Diabetes Association awarded to J.B. Collip, June 11, 1960.

Photograph of Mrs. Collip with Dr. Edward Hall, President of the University of Western Ontario, and Premier John P. Robarts, at the unveiling of a plaque in the new Medical Sciences Building commemorating J.B. Collip, Oct. 22, 1965.

J.J.R. MACLEOD, REGIUS PROFESSOR

Photograph of a drawing of J.J.R. Macleod by Joshua Smith, R.B.A. 1924.

Signed by J.J.R. Macleod and given to C.H. Best.

J.J.R. Macleod. "Cameron Prize Lectures on the Nature of Control of the Metabolism of Carbohydrates in the Animal Body." Reprinted from the British Medical Journal, Jan. 12, 1924.

These prestigious lectures were delivered at the University of Edinburgh on October 16th and 17th, 1923.

Royal Canadian Institute. To John James Rickard Macleod, Professor of Physiology, University of Toronto. May 5, 1928.

An address of appreciation presented to Macleod on his departure from Toronto to take the position of Regius Professor of Physiology at the University of Aberdeen.

C.H. Best. "The Late John James Rickard Macleod." Reprinted from the Canadian Medical Association Journal, vol. 32 (1935).

Macleod died in Aberdeen at the early age of 58 after suffering several years of ill health. In this obituary, Best, as his former student, pays tribute to his teaching skills as well as his achievements in research.

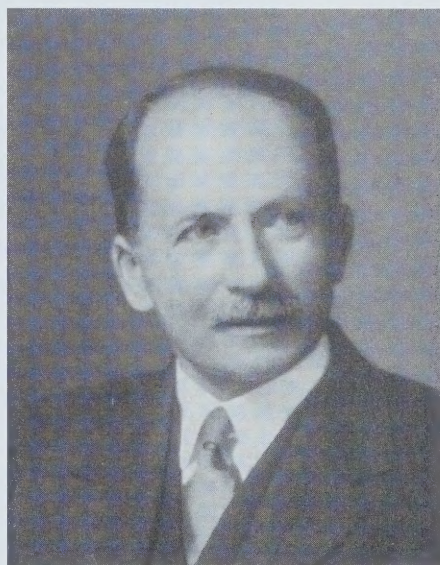
Program for the dedication of the J.J.R. Macleod Auditorium and Insulin Exhibition, Medical Sciences Auditorium, Oct. 13, 1990.

M.J. Bliss. "J.J.R. Macleod and the Discovery of Insulin." Reprinted from the Quarterly Journal of Experimental Physiology, vol. 74, (1989).

Michael J. Williams. "Aberdeen's Forgotten Nobel Prize Winner: Professor J.J.R. Macleod (1876-1935)." Reprinted from the Aberdeen University Review, no. 184 (Autumn 1990).

Two recent articles which suggest Macleod's role in the discovery of insulin should be reconsidered.

Although the original idea initiating the fundamental research was clearly Banting's, it seems very doubtful that the investigations would have reached such a successful fruition without the facilities, advice, support, and contributions provided by Professor Macleod and others. (M.J. Williams)



J.J.R. Macleod, 1930s.

SOURCES FOR THE EXHIBITION

Unless otherwise noted, the material shown in this exhibition is drawn from five manuscript collections which are held in the Thomas Fisher Rare Book Library at the University of Toronto. These collections are: the F.G. Banting Papers, the C.H. Best Papers, the J.B. Collip Papers, the W.R. Feasby Papers, and the J.J.R. Macleod Papers. Additional material has come from the collections of the Academy of Medicine, Toronto, which are now on deposit in the Thomas Fisher Rare Book Library, and from the University of Toronto Archives.

Material has also been borrowed from Dr. Henry Best, the son of C.H. Best; from the Connaught Laboratories Archives at the Balmer Neilly Library, Connaught Novo Nordisk; from the collection of Professor Michael Bliss; from the University of Alberta Archives; and from The Toronto Hospital.

The catalogue annotations utilize information contained in Professor Michael Bliss's two books: *The Discovery of Insulin* (Toronto, 1982) and *Banting, a Biography* (Toronto, 1984), as well as more recent articles on the discovery by Professor Bliss. An important additional source was Michael J. Williams's biographical account of J.J.R. Macleod entitled, "J.J.R. Macleod: the Co-discoverer of Insulin", published as Supplement no. 1 in the *Proceedings of the Royal Society of Physicians of Edinburgh*, July 1993.

ACKNOWLEDGEMENTS

Many people have helped me put together this exhibition and catalogue. My greatest debt is to Michael Bliss, Professor of History and History of Medicine, who first encouraged me to think about this project and whose two books, *The Discovery of Insulin*, and *Banting, a Biography*, have been indispensable to me in the preparation of this catalogue. I am grateful to Professor Bliss for contributing a new account of the discovery, especially written for this catalogue, and for his suggestions and support throughout. I also wish to thank Mladen Vranic, Professor of Physiology, for contributing the historical account of the University of Toronto's Physiology Department and for his support for the exhibition. Special thanks are also due to Dr. C.H. Best's son, Dr. Henry Best, for his generosity in lending many precious items and for his kindness in showing me his father's papers and sharing with me many of his memories of his father.

I am grateful for the assistance of Christopher Ruty, Archivist of the Connaught Laboratories Archives, who showed me items from Dr. Albert Fisher's collection of early insulin artifacts, recently received as a gift from Dr. Fisher. Chris also made available to me a recently rediscovered file of correspondence between J.J.R. Macleod and G.A. Clowes, and my thanks go to him and to Hugh McNaught, the head of the Balmer Neilly Library, Connaught Laboratories Ltd., for arranging for me to borrow material from these files and Dr. Fisher's collection for display.

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Just as this catalogue was going to press, I received the welcome news that the family of Elizabeth Hughes had offered to donate to this Library the original letters which Elizabeth wrote to her parents in 1922 when she came to Toronto to receive insulin from Dr. Banting. Although the news of this gift came too late to allow me to incorporate entries for the letters in the exhibition catalogue, several letters will be on display in the exhibition itself, and Professor Bliss has also quoted from them in his historical account. On behalf of the Thomas Fisher Rare Book Library, I wish to thank William T. Gossett, husband of the late Elizabeth Hughes, as well as W. Thomas Gossett, Jr., Mrs. Antoinette G. Denning, and Mrs. Elizabeth Evans Karaman, their three children, for making this generous donation.

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